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(54) Title: ADENOSINE A_3 RECEPTOR ANTAGONISTS

(57) Abstract

A pharmaceutical composition for antagonizing adenosine at adenosine A_3 receptors which comprises a 1,3–azole compound substituted on the 4– or 5– position, or both, by a pyridyl which may be substituted is provided and can be used as a prophylactic and therapeutic agent for asthma, allergosis, inflammation, and so on.

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DESCRIPTION

Adenosine A_3 Receptor Antagonists

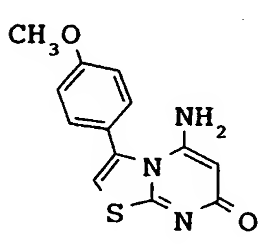
TECHNICAL FIELD

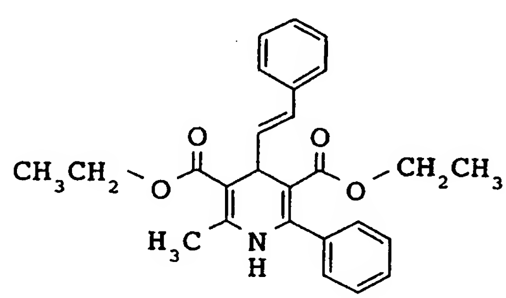
The present invention relates to an agent for antagonizing adenosine at adenosine A_3 receptors and a novel thiazole compound having a superior antagonistic activity at adenosine A_3 receptor.

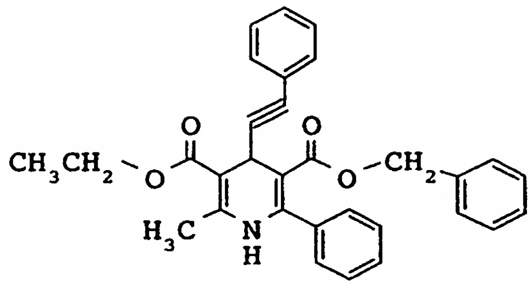
BACKGROUND ART

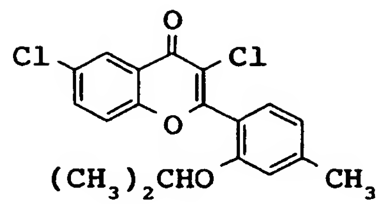
As subtypes of adenosine receptors, A_1, A_{2a}, A_{2b} and A_3 are known. Adenosine induces bronchial constriction in asthma patients, while theophylline, which is known as an antiasthmatic, antagonizes adenosine. Recently several reports showed that activation of adenosine A_3 receptors in rats promotes degranulation of mast cells [Journal of Biological Chemistry, 268, 16887-16890 (1993)], that adenosine A_3 receptors exist on peripheral blood eosinophils and that the stimulation of adenosine A_3 receptors activates phospholipase C and elevates intracellular calcium [Blood, 88, 3569-3574 (1996)].

Currently, as selective A_3 adenosine receptor antagonists, xanthine derivatives are reported in GB-A-2288733 and WO 95/11681, and the following compounds are reported in Journal of Medicinal Chemistry, 40, 2596-2608(1997).









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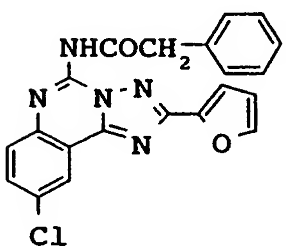

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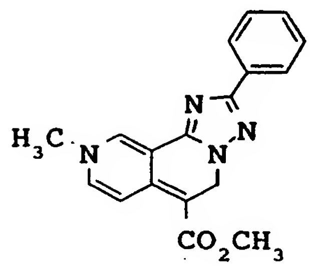
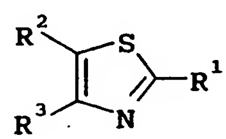


The following thiazole compounds are known.

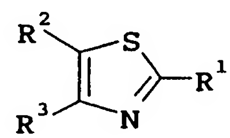
1) A thiazole derivative of the formula:



wherein R^1 represents i) cycloalkyl, ii) cyclic amino, iii) amino which may be substituted by 1 or 2 substituents selected from the group consisting of lower alkyl, phenyl, acetyl and lower alkoxycarbonylacetyl, iv) alkyl which may be substituted by a substituent selected from the group consisting of hydroxy, carboxy and lower alkoxycarbonyl or v) phenyl which may be substituted by a substituent selected from the group consisting of carboxy, 2-carboxyethenyl and 2-carboxy-1-propenyl; R^2 represents pyridyl which may be substituted by a lower alkyl; and R^3 represents phenyl which may be substituted by a substituent selected from the group consisting of lower alkoxy, lower alkyl, hydroxy, halogen and methylenedioxy, or a salt thereof, which has analgesic, anti-pyretic, anti-inflammatory, anti-ulcer,

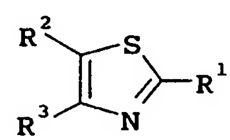
thromboxane A_2 (TXA_2) synthetase inhibitory and platelet aggregation inhibiting actions (JP-A-60-58981).

2) A 1,3-thiazole derivative of the formula:



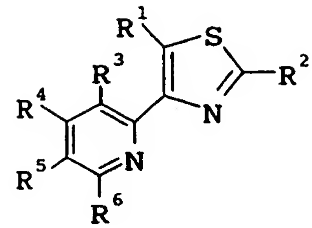
wherein R^1 represents an optionally substituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, heterocyclic group having carbon as the attachment point or amino; R^2 represents pyridyl which may be substituted by an alkyl; and R^3 represents phenyl which may be substituted, or a salt thereof, which has analgesic, anti-pyretic, anti-inflammatory, anti-ulcer, thromboxane A_2 (TXA_2) synthetase inhibitory and platelet aggregation inhibiting actions (JP-A-61-10580).

3) A 1,3-thiazole derivative of the formula:



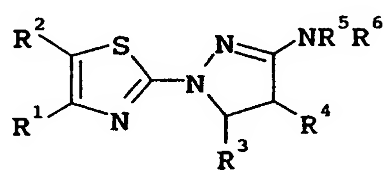
wherein R^1 represents an optionally substituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, heterocyclic group having carbon as the attachment point or amino; R^2 represents pyridyl which may be substituted by an alkyl; and R^3 represents aryl which may be substituted, or a salt thereof, which has analgesic, anti-pyretic, anti-inflammatory, anti-ulcer, thromboxane A_2 (TXA_2) synthetase inhibitory and platelet aggregation inhibiting actions (USP 4,612,321).

4) A compound of the formula:



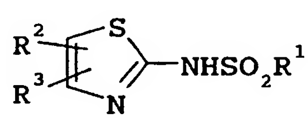
wherein R^1 is an optionally substituted phenyl, R^2 is C_{1-6} alkyl or $(CH_2)_nAr$, n is 0-2, Ar is an optionally substituted phenyl, R^3 is hydrogen or C_{1-4} alkyl, R^4 is hydrogen, C_{1-4} alkyl, etc, R^5 is hydrogen or C_{1-4} alkyl, R^6 is hydrogen, C_{1-4} alkyl, etc, or salt thereof, which has an activity of inhibiting gastric acid secretion (JP-A-07-503023, WO 93/15071).

5) A compound of the formula:



wherein R^1 is pyridyl, etc, R^2 is phenyl, etc, R^3 and R^4 are hydrogen or methyl, R^5 is methyl, etc, R^6 is hydrogen or methyl, etc, or a salt thereof, which is useful as anti-inflammatory and anti-allergic agents (DE-A-3601411).

6) A compound of the formula:



wherein R^1 is lower alkyl substituted by halogen, R^2 is pyridyl, etc, R^3 is phenyl, etc, or a salt thereof, which has anti-inflammatory, antipyretic, analgesic and anti-allergic activities (JP-A-5-70446).

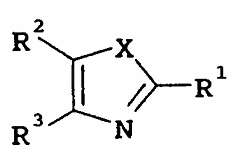
From the prior art described above, it is thought

that adenosine causes asthma through its binding to adenosine A_3 receptor, therefore A_3 adenosine receptor antagonists are expected to become a new type of antiasthma drug. Accordingly, an agent for antagonizing adenosine at adenosine A_3 receptors which has potent antagonistic activity, good bioavailability on per os administration and good metabolical stability are expected to have potent therapeutic effects for asthma, inflammation, Addison's diseases, autoallergic hemolytic anemia, Crohn's diseases, psoriasis, rheumatism and diabetes. However, as a prophylactic and therapeutic agent for adenosine A_3 receptor-related diseases, no good agent for antagonising adenosine at adenosine A_3 receptors are known in terms of potency, safety, bioavailability, and metabolic stability. Therefore a good agent for antagonising adenosine at adenosine A_3 receptor is expected to be developed.

DISCLOSURE OF INVENTION

We, the present inventors, have studied various compounds having an antagonistic activity at adenosine A_3 receptors, and as a result, have found for the first time that a 1,3-azole compound substituted on the 4- or 5-position, or both, by a pyridyl which may be substituted [hereinafter sometimes referred to briefly as compound (I)], has an unexpected, excellent selective affinity to adenosine A_3 receptor, antagonistic activity at adenosine A_3 receptor and high stability, and is therefore satisfactory as a medicine.

Compound (I) comprises, for example, a compound of the formula:



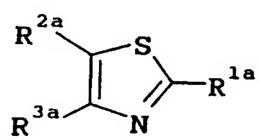
(Ia)

wherein R^1 represents a hydrogen atom, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, an amino which may be substituted or an acyl;

at least one of R^2 and R^3 represents a hydrogen atom, a pyridyl which may be substituted or an aromatic hydrocarbon group which may be substituted, and the other represents a pyridyl which may be substituted; and

X represents a sulfur atom which may be oxidized, an oxygen atom or a group of the formula: NR^4 wherein R^4 represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl;

or a salt thereof, which may be N-oxidized [hereinafter sometimes referred to briefly as compound (Ia)], and a novel compound of the formula:



(Ib)

wherein R^{1a} represents (i) an aromatic heterocyclic group which may be substituted, (ii) an amino which may be substituted by substituent(s) selected from the group consisting of a substituted carbonyl and a hydrocarbon group which may be substituted, (iii) a cyclic amino which may be substituted or (iv) an acyl;

R^{2a} represents an aromatic hydrocarbon group which may be substituted; and

R^{3a} represents a pyridyl which may be substituted, or a salt thereof [hereinafter sometimes referred to briefly as compound (Ib)] being within a scope of compound (Ia).

On the basis of these findings, the inventors have completed the present invention.

Specifically, the present invention relates to:

(1) A pharmaceutical composition for antagonizing adenosine at adenosine A_3 receptors which comprises compound (I);

(2) a composition of the above (1), wherein the 1,3-azole compound is compound (Ia);

(3) a composition of the above (2), wherein R^1 is (i) a hydrogen atom,

(ii) a C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-14} aryl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents,

(iii) a 5- to 14-membered heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents,

(iv) an amino which may be substituted by 1 or 2 substituents selected from the group consisting of

(a) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-14} aryl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents,

(b) a C_{1-6} alkylidene group which may be substituted by 1 to 5 substituents,

(c) a 5- to 14-membered heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents, and

(d) an acyl of the formula: $-(C=O)-R^5$, $-(C=O)-OR^5$, $-(C=O)-NR^5R^6$, $-(C=S)-NHR^5$ or $-SO_2-R^7$ wherein R^5 is (i') a hydrogen atom, (ii') a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-14} aryl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents or (iii') a 5- to 14-membered heterocyclic group containing 1 to 4 hetero atoms

selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents; R^6 is a hydrogen atom or C_{1-6} alkyl; and R^7 is (i') a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-14} aryl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents or (ii') a 5- to 14-membered heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents,

(v) a 5- to 7-membered non-aromatic cyclic amino optionally containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms and at least one nitrogen atom, which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl, C_{6-14} aryl, C_{1-6} alkyl-carbonyl, 5- to 10-membered aromatic heterocyclic group and oxo, or

(vi) an acyl of the formula: $-(C=O)-R^5$, $-(C=O)-OR^5$, $-(C=O)-NR^5R^6$, $-(C=S)-NHR^5$ or $-SO_2-R^7$ wherein each symbol is as defined above;

at least one of R^2 and R^3 is (i) a hydrogen atom, (ii) a pyridyl which may be substituted by 1 to 5 substituents or

(iii) a C_{6-14} aryl which may be substituted by 1 to 5 substituents in which a substituent can form, together with a neighboring substituent, a 4- to 7-membered non-aromatic carbocyclic ring;

and the other is a pyridyl which may be substituted by 1 to 5 substituents; and

X is a sulfur atom which may be oxidized, an oxygen

atom or a group of the formula: NR^4 wherein R^4 is (i) a hydrogen atom, (ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-14} aryl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents or (iii) an acyl of the formula: $-(C=O)-R^5$, $-(C=O)-OR^5$, $-(C=O)-NR^5R^6$, $-(C=S)-NHR^5$ or $-SO_2-R^7$ wherein each symbol is as defined above,

wherein the above "substituents" are selected from the group consisting of (1) halogen atoms, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated C_{2-6} alkenyl, (7) carboxy C_{2-6} alkenyl, (8) optionally halogenated C_{2-6} alkynyl, (9) optionally halogenated C_{3-6} cycloalkyl, (10) C_{6-14} aryl, (11) optionally halogenated C_{1-8} alkoxy, (12) C_{1-6} alkoxy-carbonyl-C_{1-6} alkoxy, (13) hydroxy, (14) C_{6-14} aryloxy, (15) C_{7-16} aralkyloxy,(16) mercapto, (17) optionally halogenated C_{1-6} alkylthio, (18) C_{6-14} arylthio, (19) C_{7-16} aralkylthio, (20) amino, (21) mono-C_{1-6} alkylamino, (22) mono-C_{6-14} arylamino, (23) di-C_{1-6} alkylamino, (24) di-C_{6-14} arylamino, (25) formyl, (26) carboxy, (27) C_{1-6} alkyl-carbonyl, (28) C_{3-6} cycloalkyl-carbonyl, (29) C_{1-6} alkoxy-carbonyl, (30) C_{6-14} aryl-carbonyl, (31) C_{7-16} aralkyl-carbonyl, (32) C_{6-14} aryloxy-carbonyl, (33) C_{7-16} aralkyloxy-carbonyl, (34) 5- or 6-membered heterocycle carbonyl, (35) carbamoyl, (36) mono-C_{1-6} alkyl-carbamoyl, (37) di-C_{1-6} alkyl-carbamoyl, (38) C_{6-14} aryl-carbamoyl, (39) 5- or 6-membered heterocycle carbamoyl, (40) C_{1-6} alkylsulfonyl, (41) C_{6-14} arylsulfonyl, (42) formylamino, (43) C_{1-6} alkyl-carbonylamino, (44) C_{6-14} aryl-carbonylamino, (45) C_{1-6}

alkoxy-carbonylamino, (46) C_{1-6} alkylsulfonylamino, (47) C_{6-14} arylsulfonylamino, (48) C_{1-6} alkyl-carbonyloxy, (49) C_{6-14} aryl-carbonyloxy, (50) C_{1-6} alkoxy-carbonyloxy, (51) mono-C_{1-6} alkyl-carbamoyloxy, (52) di-C_{1-6} alkyl-carbamoyloxy, (53) C_{6-14} aryl-carbamoyloxy, (54) nicotinoyloxy, (55) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl, C_{6-14} aryl, C_{1-6} alkyl-carbonyl, 5- to 10-membered aromatic heterocyclic group and oxo, (56) 5- to 10-membered aromatic heterocyclic group and (57) sulfo;

(4) a composition of the above (2), wherein R^1 is an amino which may be substituted;

(5) a composition of the above (3), wherein R^1 is an amino which may be substituted by 1 or 2 acyl of the formula: $-(C=O)-R^5$, $-(C=O)-OR^5$, $-(C=O)-NR^5R^6$, $-(C=S)-NHR^5$ or $-SO_2-R^7$;

(6) a composition of the above (3), wherein R^1 is an amino which may be substituted by 1 or 2 acyl of the formula: $-(C=O)-R^5$ or $-(C=O)-NR^5R^6$;

(7) a composition of the above (3), wherein R^1 is a 5- to 7-membered non-aromatic cyclic amino optionally containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms and at least one nitrogen atom, which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl, C_{6-14} aryl, C_{1-6} alkyl-carbonyl, 5- to 10-membered aromatic heterocyclic group and oxo;

(8) a composition of the above (2), wherein X is S;

(9) a composition of the above (2), wherein R^2 is a pyridyl which may be substituted;

(10) a composition of the above (2), wherein R^3 is a C_{6-14} aryl which may be substituted;

(11) a composition of the above (3), wherein R^1 is an amino which may be substituted by 1 or 2 acyl of the formula: $-(C=O)-R^5$ or $-(C=O)-NR^5R^6$;

R^2 is a pyridyl which may be substituted by 1 to 5 C_{1-6} alkyl;

R^3 is a C_{6-14} aryl which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy and carboxy; and

X is S;

(12) a composition of the above (2), wherein R^1 is (i) a C_{1-8} alkyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, optionally halogenated C_{1-6} alkyl, carboxy C_{2-6} alkenyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkoxy-carbonyl-C_{1-6} alkoxy, hydroxy, amino, mono-C_{1-6} alkylamino, carboxy, C_{1-6} alkoxy-carbonyl, mono-C_{1-6} alkyl-carbamoyl and C_{6-14} aryl-carbonylamino,

(ii) a 5-membered heterocyclic group,

(iii) an amino which may be substituted by 1 or 2 substituents selected from the group consisting of (1) C_{1-6} alkyl,(2) C_{6-14} aryl, (3) C_{7-16} aralkyl,(4) 6-membered heterocyclic group, (5) a C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{1-6} alkyl-carbamoyl or 5- or 6-membered heterocycle carbonyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl, C_{1-6}

alkoxy, carboxy and C_{1-6} alkoxy-carbonyl, and (6) di-C_{1-6} alkylamino-C_{1-6} alkylidene,

(iv) a 5- or 6-membered non-aromatic cyclic amino which may be substituted by C_{1-6} alkyl-carbonyl or oxo, or

(v) carboxy;

R^2 is a pyridyl which may be substituted by 1 to 3 C_{1-6} alkyl;

R^3 is a C_{6-10} aryl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, optionally halogenated C_{1-6} alkyl, carboxy C_{2-6} alkenyl, optionally halogenated C_{1-8} alkoxy, hydroxy, C_{7-16} aralkyloxy and C_{1-6} alkyl-carbonyloxy, in which the alkyl group can form, together with a neighboring alkyl group, a 5-membered non-aromatic carbocyclic ring; and

X is S;

(13) an adenosine A_3 receptor antagonist which comprises a 1,3-azole compound substituted on the 4- or 5-position, or both, by a pyridyl which may be substituted;

(14) a composition of the above (1), which is for preventing and/or treating asthma or allergosis;

(15) compound (Ib);

(16) a compound of the above (15), wherein R^{1a} is an amino which may be substituted by 1 or 2 substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkyl-carbonyl, C_{6-14} aryl-carbonyl and C_{1-6} alkyl-carbamoyl;

R^{2a} is a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, optionally halogenated C_{1-6} alkyl and

optionally halogenated C_{1-6} alkoxy; and

R^{3a} is a pyridyl;

(17) a process for producing of compound (Ib), which comprises reacting a compound of the formula:

$$R^{2a}-\underset{\displaystyle \mathrm{Hal}}{\underset{|}{\mathrm{CH}}}-COR^{3a}$$

wherein Hal represents halogen atoms and other symbols are as defined above, or a salt thereof with a compound of the formula:

$$R^{1a}-\underset{\displaystyle \mathrm{S}}{\underset{\|}{\mathrm{C}}}-NH_2$$

wherein R^{1a} is as defined above, or a salt thereof, optionally in the presence of a base;

(18) a pharmaceutical composition which comprises compound (Ib);

(19) a composition of the above (18) which is an agent for antagonizing adenosine at adenosine A_3 receptors;

(20) a composition of the above (18) which is for preventing and/or treating asthma or allergosis;

(21) a method for preventing and/or treating diseases related to adenosine A_3 receptor in mammal, which comprises administering to said mammal an effective amount of a compound of the above (1) or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable excipient, carrier or diluent; and

(22) use of a compound of the above (1) or a salt thereof for manufacturing a pharmaceutical composition for preventing and/or treating diseases related to adenosine A_3 receptor, and so forth.

In this specification, the "acyl" includes, for example, an acyl of the formula: -(C=O)-R^5, -(C=O)-OR^5,

$-(C{=}O)-NR^5R^6$, $-(C{=}S)-NHR^5$ or $-SO_2-R^7$ wherein R^5 represents a hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; R^6 represents a hydrogen atom or C_{1-6} alkyl; and R^7 represents a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted.

In the above formulae, the "hydrocarbon group" of the "hydrocarbon group which may be substituted" for R^5 includes, for example, an acyclic or cyclic hydrocarbon group such as alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, etc. Among them, C_{1-16} acyclic or cyclic hydrocarbon group is preferable.

The preferred "alkyl" is for example C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

The preferred "alkenyl" is for example C_{2-6} alkenyl such as vinyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 1-methyl-2-propenyl, 2-methyl-1-propenyl, etc.

The preferred "alkynyl" is for example C_{2-6} alkynyl such as ethynyl, propargyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-hexynyl, etc.

The preferred "cycloalkyl" is for example C_{3-6} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The preferred "aryl" is for example C_{6-14} aryl such as phenyl, 1-naphthyl, 2-naphthyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, 2-anthryl, etc.

The preferred "aralkyl" is for example C_{7-16} aralkyl such as benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc.

Examples of the "substituents" of the "hydrocarbon

group which may be substituted" for R^5 include halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{2-6} alkenyl, carboxy C_{2-6} alkenyl (e.g., 2-carboxyethenyl, 2-carboxy-2-methylethenyl, etc.), optionally halogenated C_{2-6} alkynyl, optionally halogenated C_{3-6} cycloalkyl, C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, 2-anthryl, etc.), optionally halogenated C_{1-8} alkoxy, C_{1-6} alkoxy-carbonyl-C_{1-6} alkoxy (e.g., ethoxycarbonylmethyloxy, etc.), hydroxy, C_{6-14} aryloxy (e.g., phenyloxy, 1-naphthyloxy, 2-naphthyloxy, etc.), C_{7-16} aralkyloxy (e.g., benzyloxy, phenethyloxy, etc.), mercapto, optionally halogenated C_{1-6} alkylthio, C_{6-14} arylthio (e.g., phenylthio, 1-naphthylthio, 2-naphthylthio, etc.), C_{7-16} aralkylthio (e.g., benzylthio, phenethylthio, etc.), amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, etc.), mono-C_{6-14} arylamino (e.g., phenylamino, 1-naphthylamino, 2-naphthylamino, etc.), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, ethylmethylamino, etc.), di-C_{6-14} arylamino (e.g., diphenylamino, etc.), formyl, carboxy, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, etc.), C_{3-6} cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.), C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), C_{6-14} aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl, etc.), C_{7-16} aralkyl-carbonyl (e.g., phenylacetyl, 3-phenylpropionyl, etc.), C_{6-14} aryloxy-carbonyl (e.g.,

phenoxycarbonyl, etc.), C_{7-16} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl, etc.), 5- or 6-membered heterocycle carbonyl (e.g., nicotinoyl, isonicotinoyl, thenoyl, furoyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperazin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, etc.), carbamoyl, mono-C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C_{6-14} aryl-carbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.), 5- or 6-membered heterocycle carbamoyl (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.), C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.), C_{6-14} arylsulfonyl (e.g., phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl, etc.), formylamino, C_{1-6} alkyl-carbonylamino (e.g., acetylamino, etc.), C_{6-14} aryl-carbonylamino (e.g., benzoylamino, naphthoylamino, etc.), C_{1-6} alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, etc.), C_{1-6} alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, etc.), C_{6-14} arylsulfonylamino (e.g., phenylsulfonylamino, 2-naphthylsulfonylamino, 1-naphthylsulfonylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g., acetoxy, propionyloxy, etc.), C_{6-14} aryl-carbonyloxy (e.g., benzoyloxy, naphthylcarbonyloxy, etc.), C_{1-6} alkoxy-carbonyloxy (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C_{1-6} alkyl-carbamoyloxy (e.g., methylcarbamoyloxy,

ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g., dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), C_{6-14} aryl-carbamoyloxy (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy, etc.), nicotinoyloxy, 5- to 7-membered saturated cyclic amino which may be substituted, 5- to 10-membered aromatic heterocyclic group (e.g., 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 1-indolyl, 2-indolyl, 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, 3-benzo[b]thienyl, 2-benzo[b]furanyl, 3-benzo[b]furanyl, etc.), sulfo, and so forth.

The "hydrocarbon group" may have 1 to 5, preferably 1 to 3 substituents as mentioned above at possible positions of the hydrocarbon group and, when the number of substituents is two or more, those substituents may be the same as or different from one another.

The above-mentioned "optionally halogenated C_{1-6} alkyl" includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.). Concretely mentioned is methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.

The above-mentioned "optionally halogenated C_{2-6} alkenyl" includes, for example, C_{2-6} alkenyl (e.g., vinyl, propenyl, isopropenyl, 2-buten-1-yl, 4-penten-1-

yl, 5-hexen-1-yl, etc.) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.).

The above-mentioned "optionally halogenated C_{2-6} alkynyl" includes, for example, C_{2-6} alkynyl (e.g., 2-butyn-1-yl, 4-pentyn-1-yl, 5-hexyn-1-yl, etc.) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.).

The above-mentioned "optionally halogenated C_{3-6} cycloalkyl" includes, for example, C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.). Concretely mentioned is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dichlorocyclohexyl, 2,2,3,3-tetrafluorocyclopentyl, 4-chlorocyclohexyl, etc.

The above-mentioned "optionally halogenated C_{1-8} alkoxy" includes, for example, C_{1-8} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.). Concretely mentioned is methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.

The above-mentioned "optionally halogenated C_{1-6} alkylthio" includes, for example, C_{1-6} alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.) which may have 1 to 5, preferably 1 to 3 halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.). Concretely mentioned is methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio,

pentylthio, hexylthio, etc.

The above-mentioned "5- to 7-membered saturated cyclic amino" of the "5- to 7-membered saturated cyclic amino which may be substituted" includes, for example, 5- to 7-membered saturated cyclic amino optionally containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms and at least one nitrogen atom, such as pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, thiomorpholino, tetrahydroazepin-1-yl, etc.

The "substituents" of the "5- to 7-membered saturated cyclic amino which may be substituted" include, for example, 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), C_{6-14} aryl (e.g., phenyl, 1-naphthyl, 2-naphthyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, 2-anthryl, etc.), C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, etc.), and 5- to 10-membered aromatic heterocyclic group (e.g., 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 1-indolyl, 2-indolyl, 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, 3-benzo[b]thienyl, 2-benzo[b]furanyl, 3-benzo[b]furanyl, etc.), oxo, and so forth.

The "heterocyclic group" of the "heterocyclic group which may be substituted" for R^5 includes, for example, a monovalent group formed by removing an optional hydrogen atom from a 5- to 14-membered (monocyclic, bicyclic or tricyclic) heterocyclic ring containing 1 to 4 hetero atoms of 1 or 2 species selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, preferably, (i) a 5- to 14-membered, preferably, 5- to

10-membered aromatic heterocyclic ring, (ii) a 5- to 10-membered non-aromatic heterocyclic ring and (iii) a 7- to 10-membered bridged heterocyclic ring, etc.

The above-mentioned "5- to 14-membered, preferably 5- to 10-membered aromatic heterocyclic ring" includes, for example, an aromatic heterocyclic ring such as thiophene, benzo[b]thiophene, benzo[b]furan, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, purine, 4H-quinolidine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, isoxazole, furazan, phenoxazine, etc.; and a ring as formed through condensation of those rings, preferably a monocyclic ring, with one or more, preferably one or two aromatic rings (e.g., benzene ring, etc.), etc.

The above-mentioned "5- to 10-membered non-aromatic heterocyclic ring" includes, for example, pyrrolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, morpholine, thiomorpholine, dioxazole, oxadiazoline, oxathiazole, thiadiazoline, triazoline, thiadiazole, dithiazole, etc.

The above-mentioned "7- to 10-membered bridged heterocyclic ring" includes, for example, quinuclidine, 7-azabicyclo[2.2.1]heptane, etc.

Preferable examples of the "heterocyclic group" include, for example, a 5- to 14-membered (preferably 5- to 10-membered) (monocyclic or bicyclic) heterocyclic group containing 1 to 4 hetero atoms of 1 or 2 species selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Concretely mentioned are an aromatic

heterocyclic group such as 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 3-pyrrolyl, 2-imidazolyl, 3-pyridazinyl, 3-isothiazolyl, 3-isoxazolyl, 1-indolyl, 2-indolyl, 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, 3-benzo[b]thienyl, 2-benzo[b]furanyl, 3-benzo[b]furanyl, etc; and a non-aromatic heterocyclic group such as 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-imidazolinyl, 4-imidazolinyl, 2-pyrazolidinyl, 3-pyrazolidinyl, 4-pyrazolidinyl, piperidino, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 2-piperazinyl, morpholino, thiomorpholino, etc.

Among these groups, a 5- or 6-membered heterocyclic group containing 1 to 3 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Concretely mentioned are 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, pyrazinyl, 2-pyrimidinyl, 3-pyrrolyl, 3-pyridazinyl, 3-isothiazolyl, 3-isoxazolyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-imidazolinyl, 4-imidazolinyl, 2-pyrazolidinyl, 3-pyrazolidinyl, 4-pyrazolidinyl, piperidino, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 2-piperazinyl, morpholino, thiomorpholino, etc.

The "substituents" of the "heterocyclic group which may be substituted" are the same as those mentioned above for the "substituents" of the "hydrocarbon group which may be substituted" for R^5.

The "heterocyclic group" may have 1 to 5, preferably 1 to 3 substituents as mentioned above at possible positions of the heterocyclic group and, when the number of substituents is two or more, those

substituents may be the same as or different from one another.

The "C_{1-6} alkyl" for R^6 includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

The "hydrocarbon group which may be substituted" and the "heterocyclic group which may be substituted" for R^7 include, for example, the "hydrocarbon group which may be substituted" and the "heterocyclic group which may be substituted" for R^5 above, respectively.

The "1,3-azole compound" of the "1,3-azole compound substituted on the 4- or 5-position, or both, by a pyridyl which may be substituted" in the above compound (I) includes, for example, 1,3-thiazole, 1,3-oxazole, 1,3-imidazole, and so forth.

The "substituents" of the "pyridyl which may be substituted" in the "1,3-azole compound substituted on the 4- or 5-position, or both, by a pyridyl which may be substituted" are, for example, the same as those mentioned above for the "substituents" of the "hydrocarbon group which may be substituted" for R^5.

The "pyridyl" may have 1 to 5, preferably 1 to 3 substituents as mentioned above at possible positions thereof and, when the number of substituents is two or more, those substituents may be the same as or different from one another. The ring-constituting nitrogen atom in the "pyridyl" may be oxidized (N-oxidized).

The above-mentioned "1,3-azole compound substituted on the 4- or 5-position, or both, by a pyridyl which may be substituted" may further have 1 to 4, preferably 1 to 3 substituents. When the number of substituents is two or more, those substituents may be the same as or different from one another.

Such "substituents" include, for example, a

hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, amino which may be substituted, acyl, and so forth.

The above-mentioned "hydrocarbon group which may be substituted" and the "heterocyclic group which may be substituted" includes, for example, the "hydrocarbon group which may be substituted" and the "heterocyclic group which may be substituted" for R^5 above, respectively.

The above-mentioned "amino which may be substituted" includes, for example, (1) an amino which may be substituted by 1 or 2 substituents and (2) a cyclic amino which may be substituted.

The "substituents" of the above (1) "amino which may be substituted by 1 or 2 substituents" include, for example, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, acyl, alkylidene which may be substituted, and so forth. The "hydrocarbon group which may be substituted" and the "heterocyclic group which may be substituted", include, for example, the "hydrocarbon group which may be substituted" and the "heterocyclic group which may be substituted" for R^5 above, respectively.

The above-mentioned "alkylidene" of the "alkylidene which may be substituted" include, for example, C_{1-6} alkylidene such as methylidene, ethylidene, propylidene, etc. The "substituents" of the "alkylidene which may be substituted" includes, for example, the same as those mentioned above for the "substituents" of the "hydrocarbon group which may be substituted" for R^5. The number of such substituent is 1 to 5, preferably 1 to 3.

When the number of substituents of the above "amino which may be substituted by 1 or 2 substituents" is two, those substituents may be the same as or

different from one another.

The "cyclic amino" of the above-mentioned (2) "cyclic amino which may be substituted" includes, for example, 5- to 7-membered non-aromatic cyclic amino optionally containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms and at least one nitrogen atom, such as pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, thiomorpholino, tetrahydroazepin-1-yl, imidazolidin-1-yl, 2,3-dihydro-1H-imidazol-1-yl, tetrahydro-1(2H)-pyrimidinyl, 3,6-dihydro-1(2H)-pyrimidinyl, 3,4-dihydro-1(2H)-pyrimidinyl, etc. The "substituents" of the "cyclic amino which may be substituted" include, for example, 1 to 3 of the "substituents" of the "5- to 7-membered saturated cyclic amino which may be substituted" described in detail in the foregoing referring to the "substituents" of the "hydrocarbon group which may be substituted" for R^5.

Examples of the 5- to 7-membered non-aromatic cyclic amino substituted by an oxo are 2-oxoimidazolidin-1-yl, 2-oxo-2,3-dihydro-1H-imidazol-1-yl, 2-oxotetrahydro-1(2H)-pyrimidinyl, 2-oxo-3,6-dihydro-1(2H)-pyrimidinyl, 2-oxo-3,4-dihydro-1(2H)-pyrimidinyl, etc.

Preferable example of compound (I) is compound (Ia).

The ring-constituting nitrogen atom in the 1,3-azole in compound (Ia) may be oxidized (N-oxidized).

The "hydrocarbon group which may be substituted", the "heterocyclic group which may be substituted" and the "amino which may be substituted" for R^1, include, for example, the "hydrocarbon group which may be substituted", the "heterocyclic group which may be substituted" and the "amino which may be substituted" which the above compound (I) may have, respectively.

R^1 is preferably an amino which may be substituted. More preferred is an amino which may be substituted by 1 or 2 acyl of the formula: $-(C=O)-R^5$, $-(C=O)-OR^5$, $-(C=O)-NR^5R^6$, $-(C=S)-NHR^5$ or $-SO_2-R^7$ (more preferably, $-(C=O)-R^5$ or $-(C=O)-NR^5R^6$) wherein each symbol is as defined above. Among others, especially preferred is a 5- to 7-membered non-aromatic cyclic amino optionally containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms and at least one nitrogen atom, which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl, C_{6-14} aryl, C_{1-6} alkyl-carbonyl, 5- to 10-membered aromatic heterocyclic group and oxo.

The "pyridyl which may be substituted" for R^2 or R^3 includes, for example, the "pyridyl which may be substituted" which the above compound (I) has.

The "aromatic hydrocarbon group" of the "aromatic hydrocarbon group which may be substituted" for R^2 or R^3 includes, for example, a C_{6-14} monocyclic or fused polycyclic (e.g., bi- or tri-cyclic) aromatic hydrocarbon group, etc. Concretely mentioned is C_{6-14} aryl such as phenyl, 1-naphthyl, 2-naphthyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, 2-anthryl, etc.

The "substituents" of the "aromatic hydrocarbon group which may be substituted" include, for example, the same as those mentioned above for the "substituents" of the "hydrocarbon group which may be substituted" for R^5. The number of such substituent is 1 to 5, preferably 1 to 3. When the number of substituents is two or more, those substituents may be the same as or different from one another. The two substituents (preferably alkyl groups) can form,

together with a neighboring substituent, a 4- to 7-membered (preferably, 5-membered) non-aromatic carbocyclic ring.

It is preferred case that at least one of R^2 and R^3 is a pyridyl which may be substituted or an aromatic hydrocarbon group which may be substituted, and the other is a pyridyl which may be substituted.

R^2 is preferably a pyridyl which may be substituted.

R^3 is preferably a C_{6-14} (preferably C_{6-10}) aryl which may be substituted.

The "sulfur atom which may be oxidized" for X includes S, SO and SO_2.

The "hydrocarbon group which may be substituted" for R^4 includes, for example, the "hydrocarbon group which may be substituted" for R^5 above.

X is preferably a sulfur atom which may be oxidized. More preferred is S.

In compound (Ia), preferred is a compound wherein

R^1 is an amino which may be substituted, preferably a monoacylamino;

at least one of R^2 and R^3 is a pyridyl which may be substituted or an aromatic hydrocarbon group which may be substituted, and the other is a pyridyl which may be substituted; and

X is S.

More preferred is a compound wherein

R^1 is an amino which may be substituted by 1 or 2 acyl of the formula: $-(C=O)-R^5$ or $-(C=O)-NR^5R^6$ wherein each symbol is as defined above;

R^2 is a pyridyl which may be substituted by 1 to 5 C_{1-6} alkyl;

R^3 is a C_{6-14} aryl which may be substituted by 1 to 5

substituents selected from the group consisting of halogen atoms, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy and carboxy; and X is S.

Another preferred example is a compound, wherein R^1 is (i) a C_{1-8} alkyl, C_{3-6} cycloalkyl or C_{6-14} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, optionally halogenated C_{1-6} alkyl, carboxy C_{2-6} alkenyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkoxy-carbonyl-C_{1-6} alkoxy, hydroxy, amino, mono-C_{1-6} alkylamino, carboxy, C_{1-6} alkoxy-carbonyl, mono-C_{1-6} alkyl-carbamoyl and C_{6-14} aryl-carbonylamino,
(ii) a 5-membered heterocyclic group,
(iii) an amino which may be substituted by 1 or 2 substituents selected from the group consisting of (1) C_{1-6} alkyl,(2) C_{6-14} aryl, (3) C_{7-16} aralkyl,(4) 6-membered heterocyclic group, (5) a C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{1-6} alkyl-carbamoyl or 5- or 6-membered heterocycle carbonyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl, C_{1-6} alkoxy, carboxy and C_{1-6} alkoxy-carbonyl, and (6) di-C_{1-6} alkylamino-C_{1-6} alkylidene,
(iv) a 5- or 6-membered non-aromatic cyclic amino which may be substituted by C_{1-6} alkyl-carbonyl or oxo, or
(v) carboxy;

R^2 is a pyridyl which may be substituted by 1 to 3 C_{1-6} alkyl;

R^3 is a C_{6-10} aryl which may be substituted by 1 to 3 substituents selected from the group consisting of

halogen atoms, C_{1-3} alkylenedioxy, optionally halogenated C_{1-6} alkyl, carboxy C_{2-6} alkenyl, optionally halogenated C_{1-8} alkoxy, hydroxy, C_{7-16} aralkyloxy and C_{1-6} alkyl-carbonyloxy, and the alkyl group can form, together with the neighboring alkyl group, a 5-membered non-aromatic carbocyclic ring; and X is S.

More preferred examples of compound (Ia) are N-[4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]acetamide, N-[4-(4-methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide, N-[4-(4-methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]propionamide, N-[4-(4-methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]-2-methylpropionamide, N-[4-(4-methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]butyramide, N-[4-(4-methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]benzamide, N-[4-(4-methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]nicotinamide, N-[4-(4-methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]-N'-ethylurea, N-[4-(4-methoxyphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]-N'-propylurea, 4-(4-methoxyphenyl)-2-(2-oxoimidazolidin-1-yl)-5-(4-pyridyl)-1,3-thiazole, 4-(4-methoxyphenyl)-2-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)-5-(4-pyridyl)-1,3-thiazole, 4-(4-methoxyphenyl)-2-[2-oxotetrahydro-1(2H)-pyrimidinyl)-5-(4-pyridyl)-1,3-thiazole, 4-(4-methoxyphenyl)-2-(2-oxopyrrolidin-1-yl)-5-(4-pyridyl)-1,3-thiazole, N-[4-(4-ethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-

yl]acetamide,
N-[4-(4-ethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]propionamide,
N-[4-[4-(1,1-dimethylethyl)phenyl]-5-(3-pyridyl)-1,3-thiazol-2-yl]acetamide,
N-[4-[4-(1,1-dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide,
N-[4-[4-(1,1-dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]propionamide,
N-[4-[4-(1,1-dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]-2-methylpropionamide,
N-[4-[4-(1,1-dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]butyramide,
N-[4-[4-(1,1-dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]benzamide,
N-[4-[4-(1,1-dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]nicotinamide,
N-[4-[4-(1,1-dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]-N'-ethylurea,
N-[4-[4-(1,1-dimethylethyl)phenyl]-5-(4-pyridyl)-1,3-thiazol-2-yl]-N'-propylurea,
4-[4-(1,1-dimethylethyl)phenyl]-2-(2-oxoimidazolidin-1-yl)-5-(4-pyridyl)-1,3-thiazole,
4-[4-(1,1-dimethylethyl)phenyl]-2-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)-5-(4-pyridyl)-1,3-thiazole,
4-[4-(1,1-dimethylethyl)phenyl]-2-[2-oxotetrahydro-1(2H)-pyrimidinyl]-5-(4-pyridyl)-1,3-thiazole,
4-[4-(1,1-dimethylethyl)phenyl]-2-(2-oxopyrrolidin-1-yl)-5-(4-pyridyl)-1,3-thiazole,
N-[4-(3,5-dimethylphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]acetamide,
N-[4-(3,5-dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide,
N-[4-(3,5-dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]propionamide,
N-[4-(3,5-dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-

yl]-2-methylpropionamide,
N-[4-(3,5-dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]butyramide,
N-[4-(3,5-dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]benzamide,
N-[4-(3,5-dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]nicotinamide,
N-[4-(3,5-dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]-N'-ethylurea,
N-[4-(3,5-dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]-N'-propylurea,
4-(3,5-dimethylphenyl)-2-(2-oxoimidazolidin-1-yl)-5-(4-pyridyl)-1,3-thiazole,
4-(3,5-dimethylphenyl)-2-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)-5-(4-pyridyl)-1,3-thiazole,
4-(3,5-dimethylphenyl)-2-[2-oxotetrahydro-1(2H)-pyrimidinyl]-5-(4-pyridyl)-1,3-thiazole,
4-(3,5-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)-5-(4-pyridyl)-1,3-thiazole,
N-[5-(4-pyridyl)-4-(4-trifluoromethylphenyl)-1,3-thiazol-2-yl]acetamide,
N-[5-(4-pyridyl)-4-(4-trifluoromethylphenyl)-1,3-thiazol-2-yl]propionamide,
N-[5-(4-pyridyl)-4-(4-trifluoromethylphenyl)-1,3-thiazol-2-yl]-2-methylpropionamide,
N-[5-(4-pyridyl)-4-(4-trifluoromethylphenyl)-1,3-thiazol-2-yl]benzamide,
N-[5-(4-pyridyl)-4-(4-trifluoromethylphenyl)-1,3-thiazol-2-yl]nicotinamide,
N-[5-(4-pyridyl)-4-(4-trifluoromethylphenyl)-1,3-thiazol-2-yl]-N'-ethylurea,
N-[5-(4-pyridyl)-4-(4-trifluoromethylphenyl)-1,3-thiazol-2-yl]-N'-propylurea, salts thereof, and so forth.

In compound (Ia), compound (Ib) is novel compound.

The "aromatic heterocyclic group" of the "aromatic heterocyclic group which may be substituted" for R^{1a} includes, for example, a monovalent group formed by removing an optional hydrogen atom from a 5- to 14-membered preferably 5- to 10-membered (monocyclic, bicyclic or tricyclic) aromatic heterocyclic ring containing 1 to 4 hetero atoms of 1 or 2 species selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, etc. Concretely mentioned are a monovalent group formed by removing an optional hydrogen atom from an aromatic heterocyclic ring such as thiophene, benzo[b]thiophene, benzo[b]furan, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, 1H-indazole, purine, 4H-quinolidine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazine, isothiazole, phenothiazine, isoxazole, furazan, phenoxazine, etc.; and a ring as formed through condensation of those rings, preferably a monocyclic ring, with one or more, preferably one or two aromatic rings (e.g., benzene ring, etc.), etc.

The preferred example of the "aromatic heterocyclic group" is a 5- or 6-membered aromatic heterocyclic group which may be fused with one benzene ring. Concretely mentioned are 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 3-pyrrolyl, 2-imidazolyl, 3-pyridazinyl, 3-isothiazolyl, 3-isoxazolyl, 1-indolyl, 2-indolyl, 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, 3-benzo[b]thienyl, 2-benzo[b]furanyl, 3-benzo[b]furanyl, etc. More

preferred are 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 1-indolyl, 2-benzothiazolyl, etc.

The "substituents" of the "aromatic heterocyclic group which may be substituted" and their number are the same as those mentioned above for the "substituents" of the "hydrocarbon group which may be substituted" for R^5.

The "amino" of the "amino which may be substituted by substituent(s) selected from the group consisting of a substituted carbonyl and a hydrocarbon group which may be substituted" for R^{1a} includes an amino which may be substituted by 1 or 2 substituents selected from the group consisting of a substituted carbonyl and a hydrocarbon group which may be substituted. When the number of substituents is two, those substituents may be the same as or different from one another.

The "substituted carbonyl" of the "amino which may be substituted by substituent(s) selected from the group consisting of a substituted carbonyl and a hydrocarbon group which may be substituted" includes, for example, a group of the formula: $-(C=O)-R^{5a}$, $-(C=O)-OR^{5a}$ or $-(C=O)-NR^{5a}R^{6a}$ wherein R^{5a} represents a hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted, and R^{6a} represents a hydrogen atom or a C_{1-6} alkyl.

The "hydrocarbon group which may be substituted" and the "heterocyclic group which may be substituted" for R^{5a} include, for example, the "hydrocarbon group which may be substituted" and the "heterocyclic group which may be substituted" for R^5 above, respectively.

The "C_{1-6} alkyl" for R^{6a} includes, for example, the "C_{1-6} alkyl" for R^6 above.

The examples of the "substituted carbonyl" are formyl, carboxy, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, etc.), C_{3-6} cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.), C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), C_{6-14} aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl, etc.), C_{7-16} aralkyl-carbonyl (e.g., phenylacetyl, 3-phenylpropionyl, etc.), C_{6-14} aryloxy-carbonyl (e.g., phenoxycarbonyl, etc.), C_{7-16} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethyloxycarbonyl, etc.), 5- or 6-membered heterocycle carbonyl (e.g., nicotinoyl, isonicotinoyl, thenoyl, furoyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperazin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, etc.), carbamoyl, mono-C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C_{6-14} aryl-carbamoyl (e.g., phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.), 5- or 6-membered heterocycle carbamoyl (e.g., 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.), etc.

The "hydrocarbon group which may be substituted" of the "amino which may be substituted by substituent(s) selected from the group consisting of a substituted carbonyl and a hydrocarbon group which may be substituted" for R^{1a} includes, for example, the "hydrocarbon group which may be substituted" for R^5.

The "cyclic amino which may be substituted" for R^{1a} includes, for example, the "cyclic amino which may be substituted" described in the "amino which may be

substituted" for R^1.

R^{1a} is preferably an amino which may be substituted by substituent(s) selected from the group consisting of a substituted carbonyl and a hydrocarbon group which may be substituted.

The "aromatic hydrocarbon group which may be substituted" for R^{2a} includes, for example, the "aromatic hydrocarbon group which may be substituted" for R^2 or R^3 above.

The "pyridyl which may be substituted" for R^{3a} includes, for example, the "pyridyl which may be substituted" which the above compound (I) has.

Preferred example of compound (Ib) is a compound wherein

R^{1a} is an amino which may be substituted by 1 or 2 substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkyl-carbonyl, C_{6-14} aryl-carbonyl and C_{1-6} alkyl-carbamoyl;

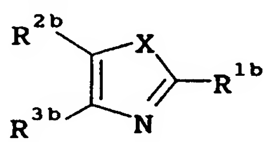
R^{2a} is a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, optionally halogenated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy; and

R^{3a} is a pyridyl.

The examples of compound (Ib) are
N-methyl[5-phenyl-4-(3-pyridyl)-1,3-thiazol-2-yl]amine,
[5-phenyl-4-(3-pyridyl)thiazol-2-yl]amine,
N-[5-phenyl-4-(3-pyridyl)thiazol-2-yl]acetoamide,
N-[5-[4-(1,1-dimethylethyl)phenyl]-4-(4-pyridyl)-1,3-thiazol-2-yl]acetamide,
N-[5-[4-(1,1-dimethylethyl)phenyl]-4-(4-pyridyl)-1,3-thiazol-2-yl]propionamide,
N-[5-[4-(1,1-dimethylethyl)phenyl]-4-(4-pyridyl)-1,3-thiazol-2-yl]nicotinamide,

N-[5-(3,5-dimethylphenyl)-4-(4-pyridyl)-1,3-thiazol-2-yl]acetamide,
N-[5-(3,5-dimethylphenyl)-4-(4-pyridyl)-1,3-thiazol-2-yl]propionamide,
N-[5-(3,5-dimethylphenyl)-4-(4-pyridyl)-1,3-thiazol-2-yl]nicotinamide, salts thereof, and so forth.

A novel compound of the formula:



(Ic)

wherein R^{1b} represents a hydrogen atom, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, an amino which may be substituted or an acyl;

R^{2b} represents a N-oxidized pyridyl which may be substituted; and

R^{3b} represents a hydrogen atom, a pyridyl which may be substituted or an aromatic hydrocarbon group which may be substituted; or a salt thereof, [hereinafter sometimes referred to briefly as compound (Ic)] is also within a scope of compound (Ia).

The "hydrocarbon group which may be substituted", the "heterocyclic group which may be substituted", the "amino which may be substituted" and the "acyl" for R^{1b} include, for example, the "hydrocarbon group which may be substituted", the "heterocyclic group which may be substituted", the "amino which may be substituted" and the "acyl" for R^1 above, respectively.

R^{1b} is preferably an amino which may be substituted. More preferred is an amino which may be substituted by 1 or 2 acyl of the formula: $-(C=O)-R^5$, $-(C=O)-OR^5$, $-(C=O)-NR^5R^6$, $-(C=S)-NHR^5$ or $-SO_2-R^7$ (more preferably, $-(C=O)-R^5$ or $-(C=O)-NR^5R^6$) wherein each

symbol is as defined above.

The "substituents" of the "N-oxidized pyridyl which may be substituted" are the same as those mentioned above for the "substituents" of the "hydrocarbon group which may be substituted" for R^5 above. The "N-oxidized pyridyl" may have 1 to 4, preferably 1 to 3 substituents as mentioned above at possible positions of the pyridyl and, when the number of substituents is two or more, those substituents may be the same as or different from one another.

The "pyridyl which may be substituted" and the "aromatic hydrocarbon group which may be substituted" for R^{3b} include, for example, the "pyridyl which may be substituted" and the "aromatic hydrocarbon group which may be substituted" for R^3 above, respectively.

R^{3b} is preferably a C_{6-14} (preferably C_{6-10}) aryl which may be substituted.

Preferred example of compound (Ic) is a compound wherein

R^{1b} is an amino which may be substituted by 1 or 2 acyl of the formula: $-(C=O)-R^5$ or $-(C=O)-NR^5R^6$ wherein each symbol is as defined above;

R^{2b} is a N-oxidized pyridyl which may be substituted by 1 to 3 C_{1-6} alkyl; and

R^{3b} is a C_{6-10} aryl which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy and carboxy.

The examples of compound (Ic) are

3-[2-acetylamino-4-(4-methoxyphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,

4-[2-acetylamino-4-(4-methoxyphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,

4-[4-(4-methoxyphenyl)-2-propionylamino-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-(4-methoxyphenyl)-2-(2-methylpropionyl)amino-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-butyrylamino-4-(4-methoxyphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-benzoylamino-4-(4-methoxyphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-(4-methoxyphenyl)-2-nicotinoylamino-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-(N'-ethylureido)-4-(4-methoxyphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-(4-methoxyphenyl)-2-(N'-propylureido)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-acetylamino-4-(4-ethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-(4-ethylphenyl)-2-propionylamino-1,3-thiazol-5-yl]pyridine 1-oxide,
3-[2-acetylamino-4-[4-(1,1-dimethylethyl)phenyl]-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-acetylamino-4-[4-(1,1-dimethylethyl)phenyl]-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-[4-(1,1-dimethylethyl)phenyl]-2-propionylamino-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-[4-(1,1-dimethylethyl)phenyl]-2-(2-methylpropionyl)amino-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-butyrylamino-4-[4-(1,1-dimethylethyl)phenyl]-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-benzoylamino-4-[4-(1,1-dimethylethyl)phenyl]-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-[4-(1,1-dimethylethyl)phenyl]-2-nicotinoylamino-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-[4-(1,1-dimethylethyl)phenyl]-2-(N'-ethylureido)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-[4-(1,1-dimethylethyl)phenyl]-2-(N'-propylureido)-1,3-thiazol-5-yl]pyridine 1-oxide,

3-[2-acetylamino-4-(3,5-dimethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-acetylamino-4-(3,5-dimethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-(3,5-dimethylphenyl)-2-propionylamino-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-(3,5-dimethylphenyl)-2-(2-methylpropionyl)amino-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-butyrylamino-4-(3,5-dimethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-benzoylamino-4-(3,5-dimethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-(3,5-dimethylphenyl)-2-nicotinoylamino-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-(3,5-dimethylphenyl)-2-(N'-ethylureido)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[4-(3,5-dimethylphenyl)-2-(N'-propylureido)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-acetylamino-4-(4-trifluoromethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-propionylamino-4-(4-trifluoromethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-(2-methylpropionyl)amino-4-(4-trifluoromethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-butyrylamino-4-(4-trifluoromethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-benzoylamino-4-(4-trifluoromethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-nicotionylamino-4-(4-trifluoromethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-(N'-ethylureido)-4-(4-trifluoromethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide,
4-[2-(N'-propylureido)-4-(4-trifluoromethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide, and so forth.

Salts of compound (I), compound (Ia), compound (Ib) or compound (Ic) include, for example, metal salts, ammonium salts, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids, etc. Preferred examples of metal salts include alkali metal salts such as sodium salts, potassium salts; alkaline earth metal salts such as calcium salts, magnesium salts, barium salts; aluminium salts, etc. Preferred examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc. Preferred examples of salts with inorganic acids include hydrochlorides, hydrobromides, nitrates, sulfates, phosphates, etc. Preferred examples of salts with organic acids include formates, acetates, trifluoroacetates, fumarates, oxalates, tartrates, maleates, citrates, succinates, malates, methanesulfonates, benzenesulfonates, p-toluenesulfonates, etc. Preferred examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc. Preferred examples of salts with acidic amino acids include aspartates, glutamates, etc.

Among others, more preferred are pharmaceutically acceptable salts. For example, for the compound having an acidic functional group in the molecule, mentioned are their inorganic salts, such as alkali metal salts (e.g., sodium salts, potassium salts, etc.), and alkaline earth metal salts (e.g., calcium salts, magnesium salts, barium salts, etc.), ammonium salts, etc.; and for the compound having a basic functional group in the molecule, mentioned are their inorganic salts such as hydrobromides, nitrates, sulfates, phosphates, etc., and organic salts such as acetates,

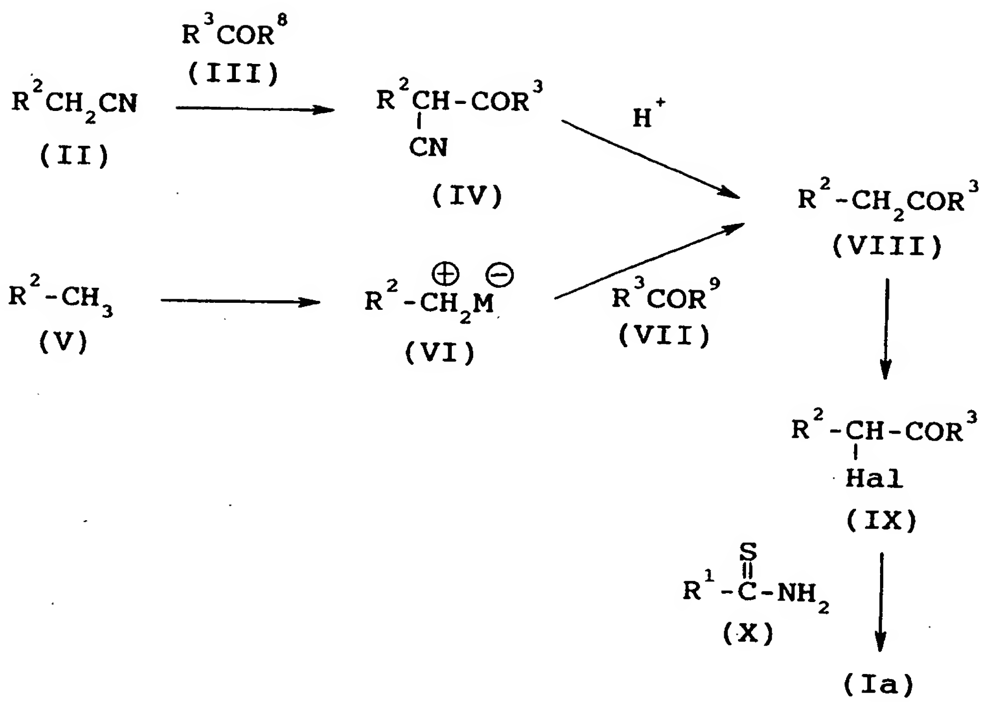
maleates, fumarates, succinates, citrates, tartrates, methanesulfonates, p-toluenesulfonates, etc.

Process for producing compound (I) (including compounds (Ia), (Ib) and (Ic)) is mentioned below.

Compound (I) can be produced in any *per se* known manner, for example, according to the methods of the following processes 1 to 3 or analogous methods thereto as well as the methods disclosed in WO 95/13067 or analogous methods thereto in case that compound (I) is 1,3-oxazole compounds, the methods disclosed in USP 3,940,486, WO 88/01169, WO 93/14081, WO 95/02591, WO 97/12876 or analogous methods thereto in case that compound (I) is 1,3-imidazole compounds, and the methods disclosed in JP-A-60-58981, JP-A-61-10580, JP-A-7-503023, WO 93/15071, DE-A-3601411, JP-A-5-70446 or analogous methods thereto in case that compound (I) is 1,3-thiazole.

Each symbol in the compounds in the following processes 1 to 3 is same as defined above. The compounds described in the following processes include their salts. For their salts, for example, referred to are the same as the salts of compound (I).

Process 1



Compounds (II), (III), (V), (VII), (XI), (XIII) and (XIV) may be purchased from commercial sources if they are available on the market or can be produced in any *per se* known manner.

Compound (IV) is produced by subjecting compound (II) to condensation with compound (III) in the presence of a base.

In compound (III), R^8 represents, for example, (i) C_{1-6} alkoxy (e.g., methoxy, ethoxy, etc.), (ii) di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, etc.), (iii) N-C_{6-10} aryl-N-C_{1-6} alkylamino (e.g., N-phenyl-N-methylamino, etc.), (iv) 3- to 7-membered cyclic amino (e.g., pyrrolidino, morpholino, methylaziridin-1-yl, etc.) which may be substituted by C_{6-10} aryl and/or C_{1-6} alkyl, etc.

The amount of compound (III) to be used is 0.5 to 3.0 mols or so, preferably 0.8 to 2.0 mols or so, relative to one mol of compound (II).

The amount of the base to be used is 1.0 to 30 mols or so, preferably 1.0 to 10 mols or so, relative to one mol of compound (II).

The "base" includes, for example, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, etc.; inorganic bases such as sodium hydroxide, potassium hydroxide, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.

This reaction is advantageously carried out in the absence of a solvent or in an inert solvent. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. Preferred are halogenated hydrocarbons, aliphatic hydrocarbons, aromatic hydrocarbons, ethers, amides, alcohols, water, and mixtures of those solvents.

The reaction temperature is generally -5 to 200 °C or so, preferably 5 to 150 °C or so. The reaction time is generally about 5 minutes to 72 hours, preferably about 0.5 to 30 hours.

The product as produced in the manner mentioned above may be applied to the next reaction while it is still crude in the reaction mixture, or may be isolated from the reaction mixture in any ordinary manner. This can be easily purified through separation means such as

recrystallization, distillation, chromatography and the like.

Compound (VIII) is produced by treating compound (IV) with an acid.

The amount of the acid to be used is 1.0 to 100 mols or so, preferably 1.0 to 30 mols or so, relative to one mol of compound (IV).

The "acids" include, for example, mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, etc.

This reaction is advantageously carried out in an inert solvent. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. Preferred are water, mixtures of water and amides, mixtures of water and alcohols, etc.

The reaction temperature is generally 20 to 200 °C or so, preferably 60 to 150 °C or so. The reaction time is generally about 30 minutes to 72 hours, preferably about 1 to 30 hours.

The product as produced in the manner mentioned above may be applied to the next reaction while it is still crude in the reaction mixture, or may be isolated from the reaction mixture in any ordinary manner. This can be easily purified through separation means such as recrystallization, distillation, chromatography and the like.

Compound (VIII) is also produced by treating compound (V) with a base followed by subjecting the resultant compound (VI) to condensation with compound (VII).

In compound (VI), M represents, for example, an alkali metal such as lithium, sodium, potassium, etc.

In compound (VII), R^9 represents, for example,

same as those mentioned above for R^8.

The amount of the base to be used is 1.0 to 30 mols or so, preferably 1.0 to 10 mols or so, relative to one mol of compound (V).

The "base" includes, for example, metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.

This reaction is advantageously carried out in the absence of a solvent or in an inert solvent. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. Preferred are aliphatic hydrocarbons, aromatic hydrocarbons, ethers, and mixtures of those solvents.

The reaction temperature is generally -78 to 60 °C or so, preferably -78 to 20 °C or so. The reaction time is generally about 5 minutes to 24 hours, preferably about 0.5 to 3 hours.

The product as produced in the manner mentioned above may be applied to the next reaction while it is still crude in the reaction mixture, or may be isolated from the reaction mixture in any ordinary manner. This can be easily purified through separation means such as recrystallization, distillation, chromatography and the like.

Compound (IX) is produced by treating compound (VIII) with a halogen. If desired, this reaction is carried out in the presence of a base or a basic salt.

The amount of the halogen to be used is 1.0 to 5.0 mols or so, preferably 1.0 to 2.0 mols or so, relative to one mol of compound (VIII).

The "halogen" includes, for example, bromine, chlorine, iodine, etc.

The amount of the base to be used is 1.0 to 10.0 mols or so, preferably 1.0 to 3.0 mols or so, relative to one mol of compound (VIII).

The "base" includes, for example, aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.

The amount of the basic salt to be used is 1.0 to 10.0 mols or so, preferably 1.0 to 3.0 mols or so, relative to one mol of compound (VIII).

The "basic salt" includes, for example, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, sodium acetate, potassium acetate, etc.

This reaction is advantageously carried out in the absence of a solvent or in an inert solvent. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. Preferred are ethers, aromatic hydrocarbons, aliphatic hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides, organic acids, aromatic amines and mixtures of those solvents.

The reaction temperature is -20 to 150 °C or so, preferably 0 to 100 °C or so. The reaction time is generally 5 minutes to 24 hours, preferably about 10 minutes to 5 hours.

The product as produced in the manner mentioned above may be applied to the next reaction while it is still crude in the reaction mixture, or may be isolated from the reaction mixture in any ordinary manner. This can be easily purified through separation means such as recrystallization, distillation, chromatography and the like.

Compound (Ia) is produced by subjecting compound (IX) to condensation with compound (X). If desired,

this reaction is carried out in the presence of a base or a basic salt.

In compound (IX), Hal represents halogens.

Compound (X) may be purchased from commercial sources if they are available on the market or can be produced according to any *per se* known methods or analogous methods thereto as well as the methods disclosed in the following process 2.

The amount of compound (X) to be used is 0.5 to 3.0 mols or so, preferably 0.8 to 2.0 mols or so, relative to one mol of compound (IX).

The amount of the base to be used is 1.0 to 30 mols or so, preferably 1.0 to 10 mols or so, relative to one mol of compound (IX).

The "base" includes, for example, basic salts such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.

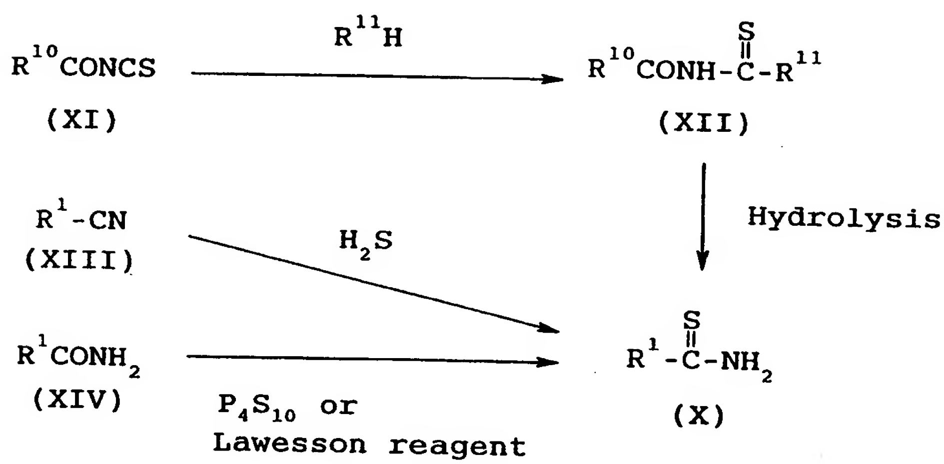
This reaction is advantageously carried out in the absence of a solvent or in an inert solvent. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. Preferred are halogenated hydrocarbons, aliphatic hydrocarbons, aromatic hydrocarbons, ethers, amides, alcohols, nitriles and mixtures of those solvents.

The reaction temperature is -5 to 200 °C or so, preferably 5 to 150 °C or so. The reaction time is generally 5 minutes to 72 hours, preferably about 0.5 to 30 hours.

The product as produced in the manner mentioned above may be applied to the next reaction while it is

still crude in the reaction mixture, or may be isolated from the reaction mixture in any ordinary manner. This can be easily purified through separation means such as recrystallization, distillation, chromatography and the like.

Process 2



Compound (XII) is produced by subjecting compound (XI) to condensation with an amine of the formula: $R^{11}H$.

R^{11} represents the "amine which may be substituted" for R^1 above.

In compound (XI), R^{10} represents an alkoxy. The "alkoxy" includes, for example, a C_{1-6} alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, etc.

The amount of the "amine" to be used is 1.0 to 30 mols or so, preferably 1.0 to 10 mols or so, relative to one mol of compound (XI).

This reaction is advantageously carried out in the absence of a solvent or in an inert solvent. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. Preferred are halogenated hydrocarbons, aliphatic

hydrocarbons, aromatic hydrocarbons, ethers, amides, alcohols, nitriles, ketones and mixtures of those solvents.

The reaction temperature is -5 to 200 °C or so, preferably 5 to 120 °C or so. The reaction time is generally 5 minutes to 72 hours, preferably about 0.5 to 30 hours.

The product as produced in the manner mentioned above may be applied to the next reaction while it is still crude in the reaction mixture, or may be isolated from the reaction mixture in any ordinary manner. This can be easily purified through separation means such as recrystallization, distillation, chromatography and the like.

Compound (X) is produced by subjecting compound (XII) to hydrolysis using an acid or a base.

The amount of the "acid" or "base" to be used is 0.1 to 50 mols or so, preferably 1 to 20 mols or so, relative to one mol of compound (XII), respectively.

The "acid" includes, for example, mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, etc; Lewis acids such as boron trichloride, boron tribromide, etc; thiols or sulfides in combination with Lewis acids; organic acids such as trifluoroacetic acid, p-toluenesulfonic acid, etc.

The "base" includes, for example, metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc; organic bases such as triethylamine, imidazole, formamidine, etc.

This reaction is advantageously carried out in the absence of a solvent or in an inert solvent. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with.

Preferred are alcohols, ethers, aromatic hydrocarbons, aliphatic hydrocarbons, halogenated hydrocarbons, sulfoxides, water and mixtures of those solvents.

The reaction time is generally 10 minutes to 50 hours, preferably about 30 minutes to 12 hours. The reaction temperature is 0 to 200 °C or so, preferably 20 to 120 °C or so.

Compound (X) is also produced by treating compound (XIII) with a hydrogen sulfide in the presence of a base.

The amount of the hydrogen sulfide to be used is 1 to 30 mols or so, relative to one mol of compound (XIII).

The amount of the "base" to be used is 1.0 to 30 mols or so, preferably 1.0 to 10 mols or so, relative to one mol of compound (XIII).

The "base" includes, for example, aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.

This reaction is advantageously carried out in the absence of a solvent or in an inert solvent. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. Preferred are halogenated hydrocarbons, aliphatic hydrocarbons, aromatic hydrocarbons, ethers, aromatic amines and mixtures of those solvents.

This reaction is carried out under atmospheric pressure or pressurized condition. The reaction temperature is -20 to 80 °C or so, preferably -10 to 30 °C or so. The reaction time is generally 5 minutes to 72 hours, preferably about 0.5 to 30 hours.

The product as produced in the manner mentioned above may be applied to the next reaction while it is still crude in the reaction mixture, or may be isolated from the reaction mixture in any ordinary manner. This can be easily purified through separation means such as recrystallization, distillation, chromatography and the like.

Compound (X) is also produced by treating compound (XIV) with a phosphorous pentasulfide or Lawesson's reagent.

The amount of the "phosphorous pentasulfide" or "Lawesson's reagent" to be used is 0.5 to 10 mols or so, preferably 0.5 to 3 mols or so, relative to one mol of compound (XIV).

This reaction is advantageously carried out in the absence of a solvent or in an inert solvent. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. Preferred are ethers, aromatic hydrocarbons, aliphatic hydrocarbons, halogenated hydrocarbons and mixtures of those solvents.

The reaction time is generally 10 minutes to 50 hours, preferably about 30 minutes to 12 hours. The reaction temperature is 0 to 150 °C or so, preferably 20 to 120 °C or so.

The product (X) may be applied to the next reaction while it is still crude in the reaction mixture, or may be isolated from the reaction mixture in any ordinary manner. This can be easily purified through separation means such as recrystallization, distillation, chromatography and the like.

In case that compound (Ia) is an acylamino derivative, the desired product can be also obtained by subjecting the corresponded amine compound to any *per*

se known acylation method.

For example, compound (Ia) wherein R^1 is an acylamino which may be substituted is produced by reacting a corresponding 2-thiazolyl amine with an acylating agent optionally in the presence of a base or an acid.

The amount of the "acylating agent" to be used is 1.0 to 5.0 mols or so, preferably 1.0 to 2.0 mols or so, relative to one mol of compound (Ia).

The "acylating agent" includes, for example, carboxylic acid or a reactive derivative thereof (e.g., acid halides, acid anhydrides, esters, etc.) correspond to the desired product.

The amount of the "base" or "acid" to be used is 0.8 to 5.0 mols or so, preferably 1.0 to 2.0 mols or so, relative to one mol of compound (Ia).

The "base" includes, for example, triethylamine, pyridine, N,N-dimethylaminopyridine, etc.

The "acid" includes, for example, methanesulfonic acid, p-toluenesulfonic acid, camphor-sulfonic acid etc.

This reaction is advantageously carried out in the absence of a solvent or in an inert solvent. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. Preferred are ethers, aromatic hydrocarbons, aliphatic hydrocarbons, amides, halogenated hydrocarbons, nitriles, sulfoxides, aromatic amines and mixtures of those solvents.

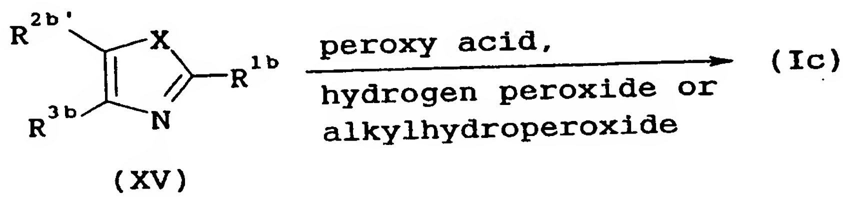
The reaction temperature is -20 to 150 °C or so, preferably 0 to 100 °C or so. The reaction time is generally 5 minutes to 24 hours, preferably about 10 minutes to 5 hours.

The product may be applied to the next reaction while it is still crude in the reaction mixture, or may be isolated from the reaction mixture in any ordinary manner. This can be easily purified through separation

means such as recrystallization, distillation, chromatography and the like.

Compound (Ic) can be also produced according to the methods of the following process 3 or analogous methods thereto.

Process 3



Compound (XV) can be produced according to any *per se* known methods or analogous methods thereto.

Compound (Ic) is produced by treating compound (XV) with a peroxy acid.

In compound (XV), $R^{2b'}$ represents a pyridyl which may be substituted. The "pyridyl which may be substituted" includes, for example, the "pyridyl which may be substituted" for R^2 above.

The amount of the "peroxy acid" to be used is 0.8 to 10 mols or so, preferably 1.0 to 3.0 mols or so, relative to one mol of compound (XV).

The "peroxy acid" includes, for example, peracetic acid, trifluoroperacetic acid, m-chloroperbenzoic acid, etc.

This reaction is advantageously carried out in the absence of a solvent or in an inert solvent. There is no particular limitation on the kind of solvent that can be used unless the reaction is interfered with. Preferred are halogenated hydrocarbons, aliphatic hydrocarbons, aromatic hydrocarbons, organic acids, ethers, amides, sulfoxides, alcohols, nitriles, ketones and mixtures of those solvents.

The reaction temperature is -20 to 130 °C or so, preferably 0 to 100 °C or so. The reaction time is generally 5 minutes to 72 hours, preferably about 0.5 to 12 hours.

Compound (Ic) is also produced by treating compound (XV) with a hydrogen peroxide or an alkylhydroperoxide, in the presence of a base, an acid or a metal oxides if desired.

The amount of the "hydrogen peroxide" or the "alkylhydroperoxide" to be used is 0.8 to 10 mols or so, preferably 1.0 to 3.0 mols or so, relative to one mol of compound (XV).

The "alkylhydroperoxide" includes, for example, tert-butylhydroperoxide, cumene hydroperoxide, etc.

The amount of the "base", the "acid" or the "metal oxides" to be used is 0.1 to 30 mols or so, preferably 0.8 to 5 mols or so, relative to one mol of compound (XV).

The "base" includes, for example, inorganic bases such as sodium hydroxide and potassium hydroxide, basic salts such as sodium carbonate and potassium carbonate, etc.

The "acid" includes, for example, mineral acids such as hydrochloric acid, sulfuric acid and perchloric acid, Lewis acids such as boron trifluoride and aluminum (III) chloride, titanium(IV) chloride, organic acids such as formic acid and acetic acid, etc.

The "metal oxides" includes, for example, vanadium oxide (V_2O_5), osmium oxide (OsO_4), tungsten oxide (WO_3), molybdenum oxide (MoO_3), selenium oxide (SeO_2), chromium oxide (CrO_3), etc.

This reaction is advantageously carried out in the absence of a solvent or in an inert solvent. There is no particular limitation on the kind of solvent that

can be used unless the reaction is interfered with. Preferred are halogenated hydrocarbons, aliphatic hydrocarbons, aromatic hydrocarbons, organic acids, ethers, amides, sulfoxides, alcohols, nitriles, ketones and mixtures of those solvents.

The reaction temperature is -20 to 130 °C or so, preferably 0 to 100 °C or so. The reaction time is generally 5 minutes to 72 hours, preferably about 0.5 to 12 hours.

The product may be applied to the next reaction while it is still crude in the reaction mixture, or may be isolated from the reaction mixture in any ordinary manner. This can be easily purified through separation means such as recrystallization, distillation, chromatography and the like.

In the above-mentioned reactions where the starting compounds are substituted by any of amino, carboxy or hydroxy, those groups may be protected by ordinary protective groups which are generally used in peptide chemistry. The protective groups may be removed after the reaction to give the disired products.

The amino-protecting group includes, for example, formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, etc.) which may be substituted, phenylcarbonyl which may be substituted, C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, etc.) which may be substituted, phenyloxycarbonyl which may be substituted, C_{7-10} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, etc.) which may be substituted, trityl which may be substituted, phthaloyl which may be substituted, etc. These substituents include, for example, halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, valeryl, etc.), nitro, etc. The number of those substituents is 1 to 3.

The carboxy-protecting group includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.) which may be substituted, phenyl which may be substituted, trityl which may be substituted, silyl which may be substituted, etc. These substituents includes, for example, halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, butylcarbonyl, etc.), nitro, C_{1-6} alkyl (e.g., methyl, ethyl, tert-butyl, etc.), C_{6-10} aryl (e.g., phenyl, naphthyl, etc.), etc. The number of those substituents is 1 to 3.

The hydroxy-protecting group includes, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.) which may be substituted, phenyl which may be substituted, C_{7-11} aralkyl (e.g., benzyl, etc.) which may be substituted, formyl which may be substituted, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, etc.) which may be substituted, phenyloxycarbonyl which may be substituted, C_{7-11} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, etc.) which may be substituted, tetrahydropyranyl which may be substituted, tetrahydrofuranyl which may be substituted, silyl which may be substituted, etc. Those substituents include, for example, halogen atoms (e.g., fluoro, chloro, bromo, iodo, etc.), C_{1-6} alkyl (e.g., methyl, ethyl, tert-butyl, etc.), C_{7-11} aralkyl (e.g., benzyl, etc.), C_{6-10} aryl (e.g., phenyl, naphthyl, etc.), nitro, etc. The number of those substituents is 1 to 4.

Those protective groups may be removed by any *per se* known methods or analogous methods thereto, such as methods using acids, bases, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate,

tetrabutylammonium fluoride, palladium acetate, etc.; and reduction, etc.

In any case, products formed in the reaction mixtures may be subjected to deprotection, acylation, alkylation, hydrogenation, oxidation, reduction, chain extension, substituents-exchange reaction and combined reactions thereof, to obtain compound (I). These methods include, for example, the methods described in "Shin Jikken Kagaku Kouza (New Edition of Lectures of Experimental Chemistry)" 14, 15 (1977) edited by Maruzen.

The above "alcohols" include, for example, methanol, ethanol, propanol, isopropanol, tert-butanol, etc.

The above "ethers" include, for example, diethyl ether, diisopropyl ether, diphenyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.

The above "halogenated hydrocarbons" include, for example, dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride, etc.

The above "aliphatic hydrocarbons" include, for example, hexane, pentane, cyclohexane, etc.

The above "aromatic hydrocarbons" include, for example, benzene, toluene, xylene, chlorobenzene, etc.

The above "aromatic amines" include, for example, pyridine, lutidine, quinoline, etc.

The above "amides" include, for example, N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide, etc.

The above "ketones" include, for example, acetone, methyl ethyl ketone, etc.

The above "sulfoxides" include, for example, dimethylsulfoxide, etc.

The above "nitriles" include, for example, acetonitrile, propionitrile, etc.

The above "organic acids" include, for example, acetic acid, propionic acid, trifluoroacetic acid, etc.

Where the products are formed in their free form in the reaction, they may be converted into their salts in any ordinary manner. Where they are formed in the form of their salts, they may be converted into free compounds or other salts in any ordinary manner. The thus-obtained compound (I) may be isolated and purified from the reaction mixtures through any ordinary means of, for example, trans-solvation, concentration, solvent extraction, fractionation, crystallization, recrystallization, chromatography and the like.

Where compound (I), (Ia), (Ib) or (Ic) exists in the reaction mixtures in the form of its configurational isomers, diastereomers, conformers or the like, they may be optionally isolated into single isomers through the separation and isolation means mentioned above. Where compound (I), (Ia), (Ib) or (Ic) is in the form of its racemates, they may be resolved into S- and R-forms through any ordinary optical resolution.

Compound (I), (Ia), (Ib) or (Ic) includes stereoisomers, depending on the type of the substituents therein, and both single isomers and mixtures of different isomers are within the scope of the present invention.

Compounds (I), (Ia), (Ib) and (Ic) may be in any form of their hydrates and non-hydrates.

The agent (pharmaceutical composition) of the present invention comprising compound (I), (Ia), (Ib) or (Ic) shows a high affinity for adenosine receptor, especially for adenosine A_3 receptor, while having low toxicity and few side effects. The agent is useful as a safe medicine.

The agent (pharmaceutical composition) of the present invention comprising compound (I), (Ia), (Ib) or (Ic) has a potent antagonistic activity on mammals (e.g., mouse, rat, hamster, rabbit, feline, canine, bovine, sheep, monkey, human, etc.), a good bioavailability on per os administration, a good metabolical stability, and therefore, it can be used for preventing and/or treating diseases that may be related to adenosine A_3 receptor, for example, asthma, allergosis, inflammation, Addison's disease, autoallergic hemolytic anemia, Crohn's disease, psoriasis, rheumatism, diabetes, and so on. Among others, preferred is for asthma, allergosis, etc.

The agent (pharmaceutical composition) of the present invention comprising compound (I), (Ia), (Ib) or (Ic) has low toxicity, and therefore, compound (I), (Ia), (Ib) or (Ic) is, either directly as it is or after having been formulated into pharmaceutical compositions along with pharmaceutically acceptable carriers in any *per se* known manner, for example, into tablets (including sugar-coated tablets, film-coated tablets), powders, granules, capsules (including soft capsules), liquid preparations, injections, suppositories, sustained release preparations, etc., safely administered orally or parenterally (e.g., locally, rectally, intravenously, etc.). In the pharmaceutical composition of the present invention, the amount of compound (I), (Ia), (Ib) or (Ic) is from 0.01 to 100 % by weight or so of the total weight of the composition. The dose of the composition varies, depending on the subject to which the composition is administered, the administration route employed, the disorder of the subject, etc. For example, as an adenosine A_3 receptor antagonist, oral composition for treating asthma, its dose for adults (body weight ca. 60 kg) may be from 0.1 to 30 mg/kg of body weight or so,

preferably from 1 to 20 mg/kg of body weight or so, in terms of the active ingredient of compound (I), (Ia), (Ib) or (Ic), and this may be administered once or several times a day.

Any ordinary organic and inorganic carrier substances that are generally used in formulating medicines are usable as the carriers for formulating the pharmaceutical compositions of the present invention. For example, employable are ordinary excipients, lubricants, binders, disintegrators, etc. for formulating solid preparations; and solvents, solubilizers, suspending agents, isotonizing agents, buffers, soothing agents, etc. for formulating liquid preparations. If desired, further employable are other additives such as preservatives, antioxidants, colorants, sweeteners, adsorbents, wetting agents, etc.

The excipients include, for example, lactose, white sugar, D-mannitol, starch, corn starch, crystalline cellulose, light silicic anhydride, etc.

The lubricants include, for example, magnesium stearate, calcium stearate, talc, colloidal silica, etc.

The binders include, for example, crystalline cellulose, white sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, starch, sucrose, gelatin, methyl cellulose, carboxymethyl cellulose sodium, etc.

The disintegrators include, for example, starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, croscarmellose sodium, carboxymethyl starch sodium, L-hydroxypropyl cellulose, etc.

The solvents include, for example, water for injections, alcohol, propylene glycol, macrogol, sesame oil, corn oil, olive oil, etc.

The solubilizers include, for example, polyethylene glycol, propylene glycol, D-mannitol,

benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.

The suspending agents include, for example, surfactants such as stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glycerin monostearate, etc.; hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, etc.

The isotonizing agents include, for example, glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol, etc.

The buffers include, for example, liquid buffers of phosphates, acetates, carbonates, citrates, etc.

The soothing agents include, for example, benzyl alcohol, etc.

The preservatives include, for example, parahydroxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc.

The antioxidants include, for example, sulfites, ascorbic acid, etc.

BEST MODE FOR CARRYING OUT THE INVENTION

The invention will be described in more detail hereinunder, with reference to the following Reference Examples, Examples, Formulation Examples and Experimental Examples, which, however, are to concretely illustrate some embodiments of the invention and are not intended to restrict the scope of the invention. Various changes and modifications can be made within the range that does not deviate the scope of the invention.

"Room temperature" as referred to in the following Reference Examples and Examples is meant to indicate a

temperature falling between 10° C and 35° C. Unless otherwise specifically indicated, "%" is by weight. The yield indicates mol/mol %.

The meanings of the abbreviations used hereinunder are as follows:

s: singlet
d: doublet
t: triplet
q: quartet
dd: double doublet
ddd: double double doublet
dt: double triplet
br: broad
J: coupling constant
Hz: Hertz
$CDCl_3$: deuterated chloroform
^{1}H-NMR: proton nuclear magnetic resonance spectrum
Me: methyl

Reference Example 1

1-(4-Methoxyphenyl)-2-(3-pyridyl)ethanone

To a stirred solution of diisopropylamine (33.2 mL) in dry tetrahydrofuran (300 mL) cooled at -78 °C, was added a solution of 1.6 M n-butyllithium in hexane (148 mL) dropwise. After addition, the resulting mixture was stirred for 10 min at the same temperature, followed by the addition of β-picoline (20 g). The resulting mixture was allowed to warm up to -10 - 0 °C. After an additional 20 min stirring, a solution of ethyl p-anisate (19.4 g) in dry tetrahydrofuran (40 mL) was added. After addition the mixture was stirred for another 1 h at ambient temperature, and water (100 mL) was added to the mixture. The solvent was removed under reduced pressure and the oily product was extracted with ethyl acetate. The extracts were washed with water, dried, and concentrated under reduced

pressure. The crystalline residue was recrystallized from ethyl acetate - isopropyl ether to afford the title compound (20.8 g, yield 85 %).
mp 71-72 °C.

Reference Example 2

Using ethyl benzoate, ethyl 3,4-dimethoxybenzoate, ethyl 3,4,5-trimethoxybenzoate, ethyl 4-(methoxymethoxy)benzoate, ethyl 4-fluorobenzoate, ethyl 4-ethylbenzoate, ethyl 3,4-methylenedioxybenzoate, methyl 5-indanecarboxylate, methyl 5,6,7,8-tetrahydro-2-naphthoic acid, methyl 1,4-benzodioxane-6-carboxylate, and methyl 2-naphthoic acid instead of using ethyl p-anisate, the below Reference Example Compounds 2-1 to 2-11 were obtained in the same manner as described in the above Reference Example 1.

Reference Example Compound 2-1:
1-Phenyl-2-(3-pyridyl)ethanone
mp 44.5-45.5° C.

Reference Example Compound 2-2:
1-(3,4-Dimethoxyphenyl)-2-(3-pyridyl)ethanone
mp 114-115° C.

Reference Example Compound 2-3:
2-(3-Pyridyl)-1-(3,4,5-trimethoxyphenyl)ethanone
mp 104-105° C.

Reference Example Compound 2-4:
1-(4-Methoxymethoxyphenyl)-2-(3-pyridyl)ethanone
mp 43-44° C.

Reference Example Compound 2-5:
1-(4-Fluorophenyl)-2-(3-pyridyl)ethanone
oil.

Reference Example Compound 2-6:
1-(4-Ethylphenyl)-2-(3-pyridyl)ethanone
mp 80-81° C.

Reference Example Compound 2-7:
1-(3,4-Methylenedioxyphenyl)-2-(3-pyridyl)ethanone

mp 98-99° C.

Reference Example Compound 2-8:
1-(5-Indanyl)-2-(3-pyridyl)ethanone
mp 55-56° C.

Reference Example Compound 2-9:
2-(3-Pyridyl)-1-(5,6,7,8-tetrahydro-2-naphthyl)ethanone
mp 65-66° C.

Reference Example Compound 2-10:
1-(1,4-Benzodioxan-6-yl)-2-(3-pyridyl)ethanone
mp 89-90° C.

Reference Example Compound 2-11:
1-(2-Naphtyl)-2-(3-pyridyl)ethanone
mp 69-70° C.

Reference Example 3

Using α-picoline, γ-picoline, and 3,5-lutidine instead of using β-picoline, the below Reference Example Compounds 3-1 to 3-5 were obtained in the same manner as described in the above Reference Example 2.

Reference Example Compound 3-1:
1-Phenyl-2-(2-pyridyl)ethanone
mp 59-60° C.

Reference Example Compound 3-2:
1-(4-Methoxyphenyl)-2-(2-pyridyl)ethanone
mp 77-78° C.

Reference Example Compound 3-3:
1-Phenyl-2-(4-pyridyl)ethanone
mp 109-110° C.

Reference Example Compound 3-4:
1-(4-Methoxyphenyl)-2-(4-pyridyl)ethanone
mp 103-104° C.

Reference Example Compound 3-5:
2-(5-Methyl-3-pyridyl)-1-phenylethanone
mp 53-54° C.

Reference Example 4

2-Cyano-2-phenyl-1-(3-pyridyl)ethanone

To a solution of ethyl nicotinate (10 g) and phenylacetonitrile (5.1 g) in tert-butyl alcohol (30 mL), was added potassium tert-butoxide (6.4 g), and the mixture was stirred at 100° C for 3 h. After cooling, the resulting mixture was dissolved in water and washed with isopropyl ether. The aqueous phase was adjusted to pH 7.0 with 2 N hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water, dried, and the solvent was evaporated. The crystalline residue was recrystallized from ethyl acetate-isopropyl ether to obtain the title compound (6.0 g, yield 62 %).
mp 148-149° C.

Reference Example 5

2-Phenyl-1-(3-pyridyl)ethanone

2-Cyano-2-phenyl-1-(3-pyridyl)ethanone (5.0 g) was dissolved in 48 % hydrobromic acid (50 mL) and the solution was stirred at 140° C for 5 h. After the mixture was cooled, the mixture was neutralized with an aqueous saturated solution of sodium hydrogen carbonate and the product was extracted with ethyl acetate. The extracts were washed with water, dried, and the solvent was evaporated. The crystalline residue was recrystallized from isopropyl ether to obtain the title compound (3.9 g, yield 88 %).
mp 61-62° C.

Reference Example 6

2-Bromo-1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone hydrobromide

1-(4-Methoxyphenyl)-2-(3-pyridyl)ethanone (6.85 g) was dissolved in acetic acid (36 mL), bromine (1.7 mL) was added to the solution and the resulting mixture was stirred at 80° C for 3 h. After the mixture was cooled with ice-water, the crude crystalline mass was

collected by filtration. The crude crystalline was recrystallized from ethanol-ethyl ether to afford the title compound (10.4 g, yield 89 %).
mp 188-195° C.

Reference Example 7

Using 1-phenyl-2-(3-pyridyl)ethanone, 1-(3,4-dimethoxyphenyl)-2-(3-pyridyl)ethanone, 2-(3-pyridyl)-1-(3,4,5-trimethoxyphenyl)ethanone, 1-(4-methoxymethoxyphenyl)-2-(3-pyridyl)ethanone, 1-(4-fluorophenyl)-2-(3-pyridyl)ethanone, 1-phenyl-2-(2-pyridyl)ethanone, 1-(4-methoxyphenyl)-2-(2-pyridyl)ethanone, 1-phenyl-2-(4-pyridyl)ethanone, 1-(4-methoxyphenyl)-2-(4-pyridyl)ethanone, 2-(5-methyl-3-pyridyl)-1-phenylethanone, 1-(4-ethylphenyl)-2-(3-pyridyl)ethanone, 1-(3,4-methylenedioxyphenyl)-2-(3-pyridyl)ethanone, 1-(5-indanyl)-2-(3-pyridyl)ethanone, 2-(3-pyridyl)-1-(5,6,7,8-tetrahydro-2-naphthyl)ethanone, 1-(1,4-benzodioxan-6-yl)-2-(3-pyridyl)ethanone, 1-(2-naphthyl)-2-(3-pyridyl)ethanone, 1-(4-methoxyphenyl)-2-(2-pyridyl)ethanone and 2-phenyl-1-(3-pyridyl)ethanone instead of using 1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone, the below Reference Example Compounds 7-1 to 7-18 were obtained in the same manner as described in the above Reference Example 6.

Reference Example Compound 7-1:
2-Bromo-1-phenyl-2-(3-pyridyl)ethanone hydrobromide
mp 208-215° C.

Reference Example Compound 7-2:
2-Bromo-1-(3,4-dimethoxyphenyl)-2-(3-pyridyl)ethanone hydrobromide
mp 191-193° C.

Reference Example Compound 7-3:
2-Bromo-2-(3-pyridyl)-1-(3,4,5-trimethoxyphenyl)ethanone hydrobromide
mp 184-186° C.

Reference Example Compound 7-4:
2-Bromo-1-(4-hydroxyphenyl)-2-(3-pyridyl)ethanone hydrobromide
The crude mixture without purification was used to next reaction.

Reference Example Compound 7-5:
2-Bromo-1-(4-fluorophenyl)-2-(3-pyridyl)ethanone hydrobromide
mp 189-191° C.

Reference Example Compound 7-6:
2-Bromo-1-phenyl-2-(2-pyridyl)ethanone hydrobromide
mp 180-181° C.

Reference Example Compound 7-7:
2-Bromo-1-(4-methoxyphenyl)-2-(2-pyridyl)ethanone hydrobromide
mp 170-171° C.

Reference Example Compound 7-8:
2-Bromo-1-phenyl-2-(4-pyridyl)ethanone hydrobromide
mp 230-232° C.

Reference Example Compound 7-9:
2-Bromo-1-(4-methoxyphenyl)-2-(4-pyridyl)ethanone hydrobromide
mp 207-209° C.

Reference Example Compound 7-10:
2-Bromo-2-(5-methyl-3-pyridyl)-1-phenylethanone hydrobromide
mp 189-193° C.

Reference Example Compound 7-11:
2-Bromo-1-(4-ethylphenyl)-2-(3-pyridyl)ethanone hydrobromide
mp 145-146° C.

Reference Example Compound 7-12:
2-Bromo-1-(3,4-methylenedioxyphenyl)-2-(3-pyridyl)ethanone hydrobromide
mp 174-175° C.

Reference Example Compound 7-13:

2-Bromo-1-(5-indanyl)-2-(3-pyridyl)ethanone hydrobromide
mp 177-178° C.

Reference Example Compound 7-14:
2-Bromo-2-(3-pyridyl)-1-(5,6,7,8-tetrahydro-2-naphthyl)ethanone hydrobromide
mp 160-162° C.

Reference Example Compound 7-15:
1-(1,4-Benzodioxan-6-yl)-2-bromo-2-(3-pyridyl)ethanone hydrobromide
oil.

Reference Example Compound 7-16:
2-Bromo-1-(2-naphthyl)-2-(3-pyridyl)ethanone hydrobromide
mp 197-199° C.

Reference Example Compound 7-17:
2-Bromo-1-(4-methoxyphenyl)-2-(2-pyridyl)ethanone hydrobromide
mp 170-171° C.

Reference Example Compound 7-18:
2-Bromo-2-phenyl-1-(3-pyridyl)ethanone hydrobromide
mp 213-218° C.

Reference Example 8
[4-(4-Methoxyphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]amine

To a suspension of thiourea (516 mg) in acetonitrile (40 mL), was added 2-bromo-1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone hydrobromide (2.5 g), and then triethylamine (0.95 mL) was added slowly dropwise to the mixture with stirring. After addition, the mixture was stirred at reflux for 3 h. After cooling, the crude crystalline was collected by filtration. The crystalline was washed with an aqueous saturated solution of sodium hydrogen carbonate, water, ethanol, and ethyl ether, in that order, and dried.

The obtained crude crystalline was recrystallized from tetrahydrofuran to give the title compound (1.5 g, yield 90 %).
mp 265-266° C.

Reference Example 9
N-Methyl[4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]amine

To a suspension of N-methylthiourea (242 mg) in acetonitrile (18 mL), was added 2-bromo-1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone hydrobromide (1.0 g) and then triethylamine (0.4 mL) was added slowly dropwise to the mixture. After addition, the resulting mixture was stirred at reflux for 3 h, and the solvent was evaporated. An aqueous saturated solution of sodium hydrogen carbonate was added to the residue and extracted with ethyl acetate. The extracts were washed with water, dried, and the solvent was evaporated. The crystalline residue was recrystallized from ethyl acetate-isopropyl ether to afford the title compound (650 mg, yield 85 %).
mp 158-159° C.

Reference Example 10
N-[4-(4-Methoxyphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]acetamide

Using [(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]amine as starting material, the title compound was obtained in the same manner as described in below Example 3. Yield 82 %.
mp 208-210° C.

Reference Example 11
2-(4-Acetylpiperazin-1-yl)-4-(4-methoxyphenyl)-5-(3-pyridyl)-1,3-thiazole

To a solution of 1-piperazinecarbothioamide (387

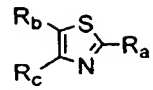
mg) in acetonitrile (15 mL), was added 2-bromo-1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone hydrobromide (1.0 g), and then triethylamine (0.4 mL) was added slowly dropwise to the resulting mixture. After addition the mixture was stirred at reflux for 3 h and the solvent was evaporated. An aqueous saturated solution of sodium hydrogen carbonate was added to the residue and extracted with ethyl acetate. The extracts were washed with water, dried and the solvent was evaporated. The residue was dissolved in pyridine (2 mL) and acetyl chloride (0.3 mL) was added to the solution under ice cooling. The resulting mixture was stood at room temperature for 1 h. The reaction mixture was poured into ice-water and the product was extracted with ethyl acetate. The extracts were washed with water , dried, and the solvent was evaporated. The residue was purified using silica-gel column chromatography (ethyl acetate-methanol, 9:1) to give the title compound (300 mg, yield 28 %).
oil.

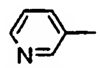
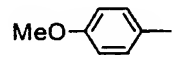
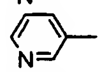
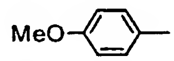
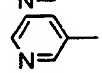
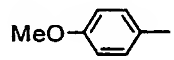
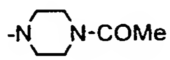
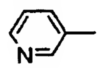
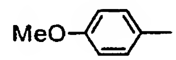
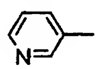
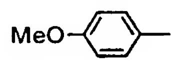
Reference Example 12
[4-(4-Methoxyphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]amine hydrochloride

[4-(4-Methoxyphenyl)-5-(3-pyridyl)-1,3-thiazol-2-yl]amine (200 mg) was dissolved in 1 % methanol solution of hydrogen chloride (3.2 mL), and the solvent was evaporated. The crude crystalline was recrystallized from methanol-ethyl acetate to give the title compound (180 mg, yield 80 %).
mp 145-150° C.

The chemical structures of the compounds obtained in the Reference Examples 8 to 12 are shown in Table 1.

Table 1

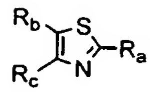


Ref. Ex. Compd.	R_a	R_b	R_c	Additive
8	$-NH_2$			
9	-NHMe			
10	-NHCOMe			
11				
12	$-NH_2$			HCl

Reference Example 13

The following Reference Example Compounds 13-1 to 13-106 shown in Tables 2 to 7 were obtained in the same manner as described in the above References 8 to 12, JP-A-61-10580 and USP 4,612,321.

Table 2



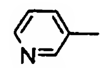
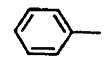
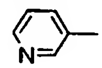
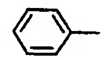
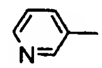
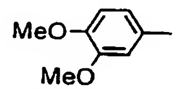
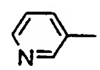
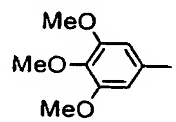
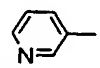
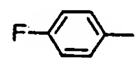
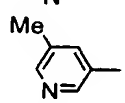
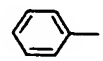
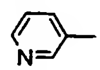
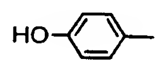
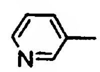
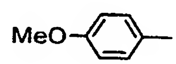
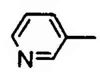
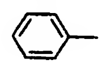
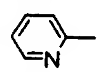
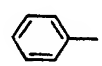
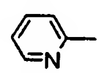
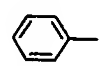
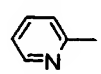
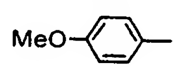
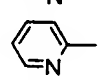
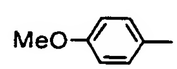
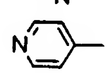
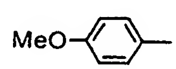
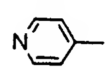
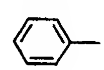
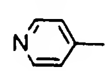
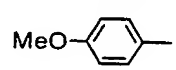
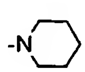
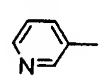
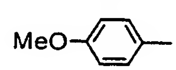
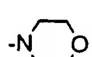
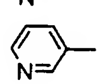
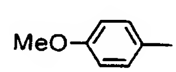
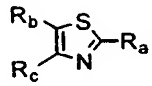
Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
13-1	-NHMe			168-169
13-2	$-NH_2$			253-254
13-3	$-NH_2$			240-241
13-4	$-NH_2$			168-169
13-5	-NHMe			157-158
13-6	-NHMe			205-206
13-7	$-NH_2$			266-268
13-8	$-NHCOCH_2COOCH_2Me$			201-202
13-9	$-NHCOCH_2COOMe$			185-186
13-10	$-NH_2$			236-237
13-11	-NHMe			215-216
13-12	-NHMe			214-215
13-13	$-NH_2$			217-218
13-14	$-NH_2$			282-284
13-15	$-NH_2$			248-250
13-16	-NHMe			177-178
13-17				130-131
13-18				134-135

Table 3



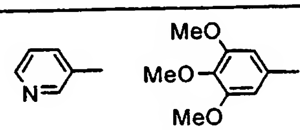
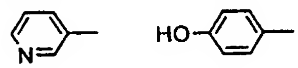
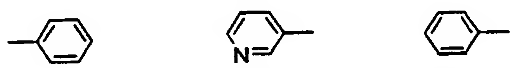
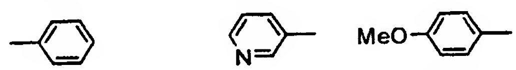
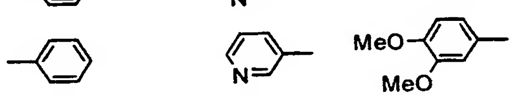
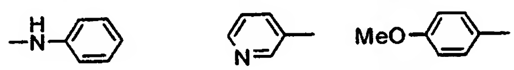
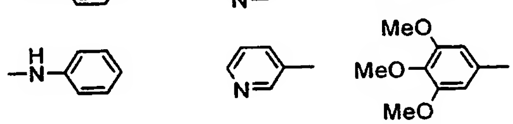
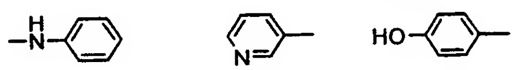
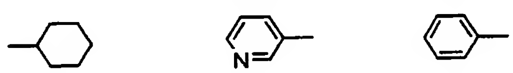
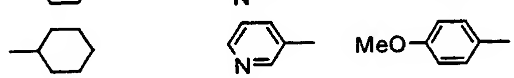
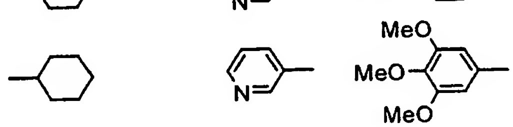
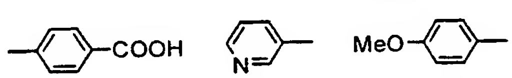
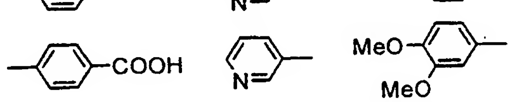
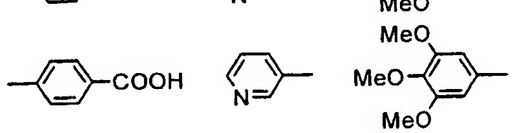
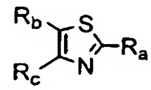
Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
13-19	$-CH_2Me$			84-84.5
13-20	$-CH_2Me$			59-60
13-21	$-CH_2Me$			174-175
13-22	-Me			113-114
13-23	$-CH_2Me$			83-84
13-24				135-136
13-25				104-105
13-26				96-98
13-27				195-196
13-28				211-213
13-29				280-282
13-30				100-101
13-31				92-93
13-32				111-112
13-33				264-265
13-34				245-246
13-35				247-248

Table 4



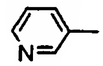
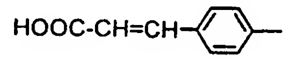
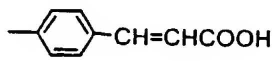
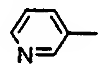
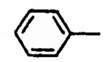
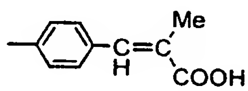
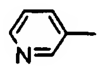
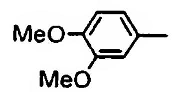
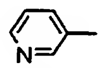
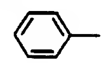
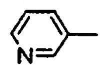
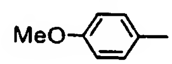
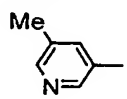
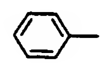
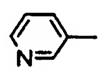
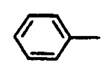
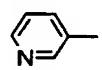
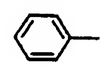
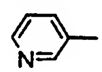
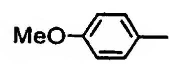
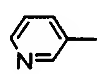
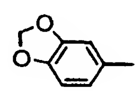
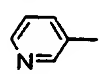
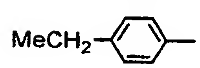
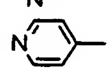
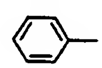
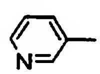
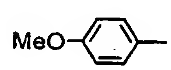
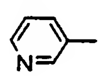
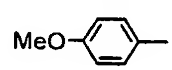
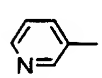
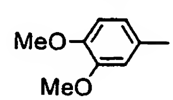
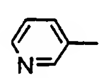
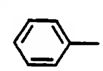
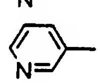
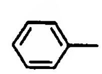
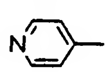
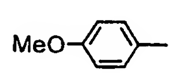
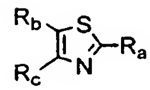
Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
13-36	-Me			208-209
13-37				255-256
13-38				225-226
13-39	$-(CH_2)_3COOH$			143-144
13-40	$-(CH_2)_3COOH$			163-164
13-41	$-(CH_2)_3COOH$			134-135
13-42	$-(CH_2)_8COOH$			112-113
13-43	$-(CH_2)_4OH$			51-52
13-44	$-NHCH_2Me$			154-155
13-45	-NHMe			187-188
13-46	-NHMe			124-125
13-47	-NHMe			191-192
13-48	$-N(CH_2Me)_2$			oil
13-49	$-NMe_2$			oil
13-50	$-CH_2Me$			oil
13-51	$-CH_2Me$			oil
13-52	$-(CH_2)_3Me$			oil
13-53	$-CH_2Me$			oil

Table 5



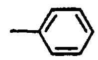
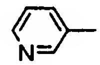
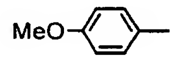
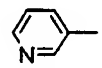
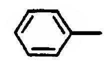
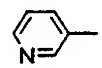
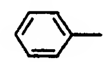
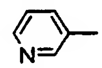
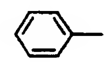
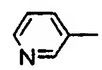
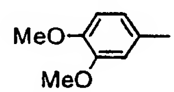
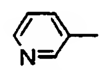
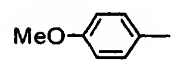
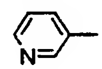
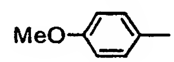
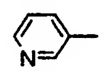
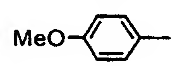
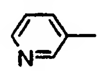
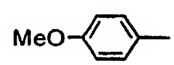
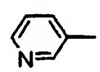
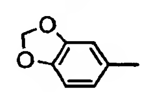
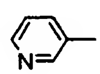
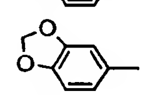
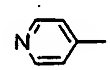
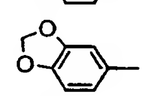
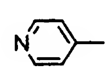
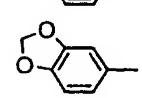
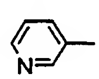
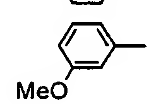
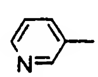
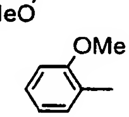
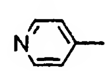
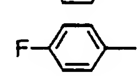
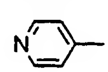
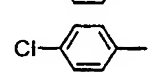
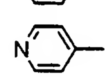
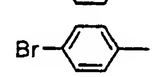
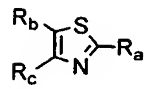
Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
13-54				104-105
13-55	$-CH_2COOH$			oil
13-56	$-(CH_2)_3COOMe$			oil
13-57	$-(CH_2)_5COOH$			oil
13-58	$-(CH_2)_5COOH$			oil
13-59	$-(CH_2)_4OH$			oil
13-60	$-(CH_2)_6OH$			oil
13-61	$-(CH_2)_2Me$			oil
13-62	$-CHMe_2$			oil
13-63	$-NMe_2$			76-77
13-64	$-N(CH_2Me)_2$			97-98
13-65	-NHMe			234-235
13-66	$-NMe_2$			144-145
13-67	-NHMe			146-147
13-68	-NHMe			153-154
13-69	-NHMe			205-206
13-70	-NHMe			224-225
13-71	-NHMe			206-207

Table 6



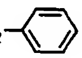
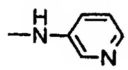
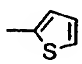
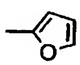
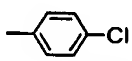
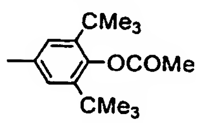
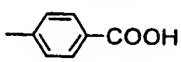
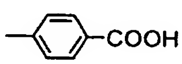
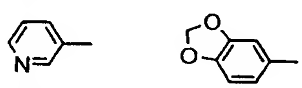
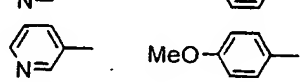
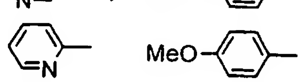
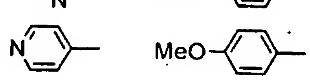
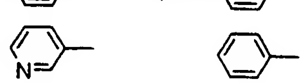
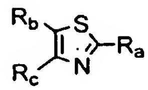
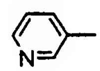
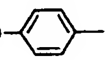
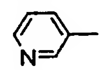
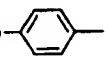
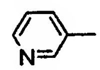
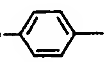
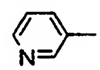
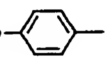
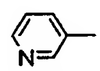
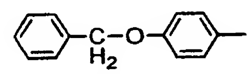
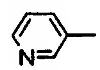
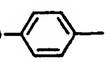
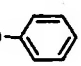
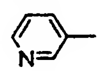
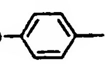
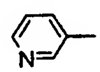
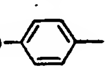
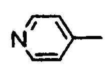
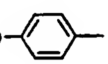
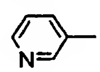
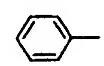
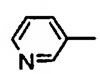
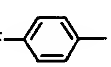
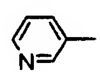
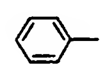
Ref. Ex. Compd.	R_a	R_b	R_c	Additive	mp / °C
13-72	-NHMe				191-192
13-73	-NHMe				168-169
13-74	-NHMe				172-173
13-75	-NHCH$_2$CH$_2$- 				126-127
13-76					222-223
13-77					132-133
13-78					90-91
13-79					148-149
13-80					180-181
13-81					240-241
13-82					258-259
13-83	-NMe$_2$				85-86
13-84	-N(CH$_2$Me)$_2$				56-57
13-85	-CH$_2$NH$_2$				oil
13-86	-CH$_2$NHMe				oil
13-87	-NHCOMe			HCl	214-217
13-88	-NHCOMe				228-231
13-89	-NHCOMe			HCl	275-278
13-90	-NHCOCH$_2$Me			HCl	248-251

Table 7



Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
13-91	-NHCOCH$_2$Me		MeO- 	196-199
13-92	-NHCOCHMe$_2$		MeO- 	213-216
13-93	-NH$_2$		Me(H$_2$C)$_3$O- 	212-215
13-94	-NHCOMe		Me(H$_2$C)$_3$O- 	230-233
13-95	-NH$_2$			186-189
13-96	-NHCOMe		MeOCO- 	230-234
13-97	-NHCO- 		MeO- 	275-278
13-98	-NHCOMe		HO- 	287-292
13-99	-NMeCOMe		MeO- 	169-172
13-100	-NHCOMe			222-224
13-101	-NHCOMe		F- 	175-178
13-102	-N=CHNMe$_2$			118-120

Reference Example 14

N-(4-Chlorobenzoyl)propyleneimine

A solution of propyleneimine (12.3 mL) in tetrahydrofuran (160 mL) was added to an 1N aqueous sodium hydroxide solution. To the mixture was added dropwise 4-chlorobenzoyl chloride (25 g) at 0° C. After addition, the mixture was stirred for additional 30 min. The reaction mixture was extracted with ethyl acetate.

The extract was dried, concentrated under reduced pressure to afford the title compound (24.9 g, yield 89 %).
oil.
^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, J= 5.5 Hz), 2.15 (1H, d, J= 2.9 Hz), 2.51-2.66 (2H, m), 7.39-7.47 (2H, m), 7.93-8.01 (2H, m).

Reference Example 15

Using 3-chlorobenzoyl chloride, 2-chlorobenzoyl chloride, 2-methylbenzoyl chloride, 3-methylbenzoyl chloride, 4-methylbenzoyl chloride, 2-methoxybenzoyl chloride, 3-methoxybenzoyl chloride, 4-ethylbenzoyl chloride, 4-(1-methylethyl)benzoyl chloride, 4-(1,1-dimethylethyl)benzoyl chloride, 4-propylbenzoyl chloride, 4-butylbenzoyl chloride, 4-hexylbenzoyl chloride, 4-trifluoromethoxybenzoyl chloride, 4-trifluoromethylbenzoyl chloride, 3,4-dimethoxybenzoyl chloride, 3,4-dimethylbenzoyl chloride, 3,5-dimethylbenzoyl chloride, 3,4-methylenedioxybenzoyl chloride and 2-naphthoyl chloride instead of using 4-chlorobenzoyl chloride, the below Reference Example Compounds 15-1 to 15-20 were obtained in the same manner as described in the above Reference Example 14.
Reference Example Compound 15-1:
N-(3-Chlorobenzoyl)propyleneimine
oil.
^{1}H-NMR ($CDCl_3$) δ : 1.40 (3H, d, J= 5.1 Hz), 2.17 (1H, d, J= 3.3 Hz), 2.53-2.68 (2H, m), 7.40 (1H, dd, J= 8.1, 7.7 Hz), 7.53 (1H, ddd, J= 8.1, 2.2, 1.5 Hz), 7.90 (1H, dt, J= 7.7, 1.5 Hz), 8.00 (1H, dd, J= 2.2, 1.5 Hz).
Reference Example Compound 15-2:
N-(2-Chlorobenzoyl)propyleneimine
oil.
^{1}H-NMR ($CDCl_3$) δ : 1.30 (3H, d, J= 5.1 Hz), 2.12 (1H, d, J= 3.3 Hz), 2.53 (1H, d, J= 5.5 Hz), 2.56-2.68 (1H, m),

7.28-7.48 (3H, m), 7.75-7.81 (1H, m).

Reference Example Compound 15-3:

N-(2-Methylbenzoyl)propyleneimine

oil.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (3H, d, J= 5.5 Hz), 2.08 (1H, d, J= 3.3 Hz), 2.43-2.57 (5H, m), 7.20-7.31 (2H, m), 7.33-7.43 (1H, m), 7.89 (1H, d, J= 7.7 Hz).

Reference Example Compound 15-4:

N-(3-Methylbenzoyl)propyleneimine

oil.

^{1}H-NMR ($CDCl_3$) δ : 1.39 (3H, d, J= 5.5 Hz), 2.14 (1H, d, J= 3.3 Hz), 2.41 (3H, s), 2.51-2.66 (2H, m), 7.32-7.39 (2H, m), 7.79-7.87 (2H, m).

Reference Example Compound 15-5:

N-(4-Methylbenzoyl)propyleneimine

oil.

^{1}H-NMR ($CDCl_3$) δ : 1.39 (3H, d, J= 5.5 Hz), 2.12 (1H, d, J= 2.9 Hz), 2.42 (3H, s), 2.50-2.62 (2H, m), 7.25 (2H, d, J= 8.1 Hz), 7.92 (2H, d, J= 8.1 Hz).

Reference Example Compound 15-6:

N-(2-Methoxybenzoyl)propyleneimine

oil.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (3H, d, J= 5.5 Hz), 2.10 (1H, d, J= 3.3 Hz), 2.50 (1H, d, J= 5.9Hz), 2.53-2.65 (1H, m), 3.90 (3H, s), 6.95-7.05 (2H, m), 7.41-7.52 (1H, m) 7.81-7.88 (1H, m).

Reference Example Compound 15-7:

N-(3-Methoxybenzoyl)propyleneimine

oil.

^{1}H-NMR ($CDCl_3$) δ : 1.40 (3H, d, J= 5.9 Hz), 2.14 (1H, d, J= 2.9 Hz), 2.52-2.65 (2H, m), 3.86 (3H, s), 7.10 (1H, ddd, J= 8.4, 2.6, 1.1 Hz), 7.37 (1H, dd, J= 8.4, 7.3 Hz), 7.55 (1H, dd, J= 2.6, 1.5 Hz), 7.63 (1H, ddd, J= 7.3, 1.5, 1.1 Hz).

Reference Example Compound 15-8:

N-(4-Ethylbenzoyl)propyleneimine
oil.

^{1}H-NMR ($CDCl_3$) δ : 1.27 (3H, t, J= 7.6 Hz), 1.39 (3H, d, J= 5.5 Hz), 2.13 (1H, d, J= 3.3 Hz), 2.50-2.61 (2H, m), 2.71 (2H, q, J= 7.6 Hz), 7.28 (2H, d, J= 7.7 Hz), 7.95 (2H, d, J= 7.7 Hz).

Reference Example Compound 15-9:
N-[4-(1-Methylethyl)benzoyl]propyleneimine
oil.

^{1}H-NMR ($CDCl_3$) δ : 1.28 (6H, d, J= 7.0 Hz), 1.40 (3H, d, J= 5.5 Hz), 2.13 (1H, d, J= 3.3 Hz), 2.50-2.64 (2H, m), 2.90-3.05 (1H, m), 7.31 (2H, d, J= 8.2 Hz), 7.96 (2H, d, J= 8.2 Hz).

Reference Example Compound 15-10:
N-[4-(1,1-Dimethylethyl)benzoyl]propyleneimine
oil.

^{1}H-NMR ($CDCl_3$) δ : 1.35 (9H, s), 1.41 (3H, d, J= 5.5Hz), 2.12 (1H, d, J= 2.9 Hz), 2.51-2.64 (2H, m), 7.47 (2H, d, J= 8.8 Hz), 7.96 (2H, d, J= 8.8Hz).

Reference Example Compound 15-11:
N-(4-Propylbenzoyl)propyleneimine
oil.

^{1}H-NMR ($CDCl_3$) δ : 0.96 (3H, t, J= 7.3 Hz), 1.39 (3H, d, J= 5.5 Hz), 1.57-1.75 (2H, m), 2.12 (1H, d, J= 3.3 Hz), 2.50-2.59 (2H, m), 2.65 (2H, t, J= 7.7 Hz), 7.26 (2H, d, J= 8.1 Hz), 7.94 (2H, d, J= 8.1 Hz).

Reference Example Compound 15-12:
N-(4-Butylbenzoyl)propyleneimine
oil.

^{1}H-NMR ($CDCl_3$) δ : 0.94 (3H, t, J= 7.1 Hz), 1.26-1.47 (5H, m), 1.54-1.73 (2H, m), 2.12 (1H, d, J= 2.9 Hz), 2.51-2.62 (2H, m), 2.67 (2H, t, J= 7.7 Hz), 7.26 (2H, d, J= 8.1 Hz), 7.94 (2H, d, J= 8.1 Hz).

Reference Example Compound 15-13:
N-(4-Hexylbenzoyl)propyleneimine

oil.
^{1}H-NMR ($CDCl_3$) δ : 0.89 (3H, t, J= 6.6 Hz), 1.24-1.38 (6H, m), 1.39 (3H, d, J= 5.5 Hz), 1.56-1.68 (2H, m), 2.12 (1H, d, J= 3.3 Hz), 2.51-2.61 (2H, m), 2.66 (2H, t, J= 7.7 Hz), 7.26 (2H, d, J= 8.1 Hz), 7.94 (2H, d, J= 8.1 Hz).

Reference Example Compound 15-14:
N-(4-Trifluoromethoxybenzoyl)propyleneimine
oil.
^{1}H-NMR ($CDCl_3$) δ : 1.40 (3H, d, J= 5.5 Hz), 2.16 (1H, d, J= 3.3 Hz), 2.53-2.68 (2H, m), 7.29 (2H, d, J= 9.0 Hz), 8.08 (2H, d, J= 9.0 Hz).

Reference Example Compound 15-15:
N-(4-Trifluoromethylbenzoyl)propyleneimine
oil.
^{1}H-NMR ($CDCl_3$) δ : 1.40 (3H, d, J= 5.5 Hz), 2.19 (1H, d, J= 3.7 Hz), 2.54-2.70 (2H, m), 7.73 (2H, d, J= 8.0 Hz), 8.13 (2H, d, J= 8.0 Hz).

Reference Example Compound 15-16:
N-(3,4-Dimethoxybenzoyl)propyleneimine
oil.
^{1}H-NMR ($CDCl_3$) δ : 1.41 (3H, d, J= 5.5 Hz), 2.12 (1H, d, J= 3.3 Hz), 2.51-2.63 (2H, m), 3.94 (3H, s), 3.95 (3H, s), 6.92 (1H, d, J= 8.5 Hz), 7.56 (1H, d, J= 2.2 Hz), 7.69 (1H, dd, J= 8.5, 2.2 Hz).

Reference Example Compound 15-17:
N-(3,4-Dimethylbenzoyl)propyleneimine
oil.
^{1}H-NMR ($CDCl_3$) δ : 1.39 (3H, d, J= 5.5 Hz), 2.12 (1H, d, J= 3.3 Hz), 2.32 (6H, s), 2.49-2.61 (2H, m), 7.21 (1H, d, J= 7.7 Hz), 7.77 (1H, dd, J= 7.7, 1.8 Hz), 7.80 (1H, d, J= 1.8 Hz).

Reference Example Compound 15-18:
N-(3,5-Dimethylbenzoyl)propyleneimine
oil.

^{1}H-NMR ($CDCl_3$) δ : 1.39 (3H, d, J= 5.5 Hz), 2.13 (1H, d, J= 3.7 Hz), 2.37 (6H, s), 2.47-2.62 (2H, m), 7.19 (1H, s), 7.64 (2H, s).

Reference Example Compound 15-19:
N-(3,4-Methylenedioxybenzoyl)propyleneimine
oil.

^{1}H-NMR ($CDCl_3$) δ : 1.38 (3H, d, J= 4.9 Hz), 2.11 (1H, d, J= 3.1 Hz), 2.48-2.64 (2H, m), 6.05 (2H, s), 6.86 (1H, d, J= 8.2 Hz), 7.48 (1H, d, J= 1.7 Hz), 7.65 (1H, dd, J= 8.2, 1.7 Hz).

Reference Example Compound 15-20:
N-(2-Naphthoyl)propyleneimine
oil.

^{1}H-NMR ($CDCl_3$) δ : 1.44 (3H, d, J= 5.5 Hz), 2.22 (1H, d, J= 3.3 Hz), 2.57-2.84 (2H, m), 7.50-7.65 (2H, m), 7.85-8.00 (3H, m), 8.06 (1H, dd, J= 8.6, 1.5 Hz), 8.59 (1H, s).

Reference Example 16
1-(2-Chlorophenyl)-2-(4-pyridyl)ethanone

To a stirred solution of diisopropylamine (15.4 mL) in dry tetrahydrofuran (100 mL) cooled at -50°C, was added a solution of 1.6 M n-butyllithium in hexane (69 mL) dropwise. After addition, the resulting mixture was stirred for 10 min at the same temperature, followed by the addition of a solution of γ-picoline (20 g) in dry tetrahydrofuran (10 mL) at -30°C. After an additional 1 h stirring, a solution of N-(2-chlorobenzoyl)propyleneimine (20 g) in dry tetrahydrofuran (10 mL) was added dropwise to the resulting mixture at -10°C. After addition the mixture was stirred for another 2 h at ambient temperature. Water (100 mL) was added to the mixture and extracted with ethyl acetate. The extract was washed with water, dried, and concentrated under reduced pressure. The

residue was purified using silica-gel column chromatography (hexane-ethyl acetate, 1:1) to give the title compound (16.4 g, yield 71 %).
oil.
^{1}H-NMR ($CDCl_3$) δ : 4.28 (2H, s), 7.20 (2H, d, J= 6.2 Hz), 7.28-7.39 (1H, m), 7.41-7.48 (3H, m), 8.56 (2H, d, J= 6.2 Hz).

Reference Example 17

Using N-(3-chlorobenzoyl)propyleneimine, N-(4-chlorobenzoyl)propyleneimine, N-(2-methylbenzoyl)propyleneimine, N-(3-methylbenzoyl)propyleneimine, N-(4-methylbenzoyl)propyleneimine, N-(2-methoxybenzoyl)propyleneimine, N-(3-methoxybenzoyl)propyleneimine, N-(4-ethylbenzoyl)propyleneimine, N-[4-(1-methylethyl)benzoyl]propyleneimine, N-[4-(1,1-dimethylethyl)benzoyl]propyleneimine, N-(4-propylbenzoyl)propyleneimine, N-(4-butylbenzoyl)propyleneimine, N-(4-hexylbenzoyl)propyleneimine, N-(4-trifluoromethoxybenzoyl)propyleneimine, N-(4-trifluoromethylbenzoyl)propyleneimine, N-(3,4-dimethoxybenzoyl)propyleneimine, N-(3,4-dimethylbenzoyl)propyleneimine, N-(3,5-dimethylbenzoyl)propyleneimine, N-(3,4-methylenedioxybenzoyl)propyleneimine and N-(2-naphthoyl)propyleneimine instead of using N-(2-chlorobenzoyl)propyleneimine, the below Reference Example Compounds 17-1 to 17-20 were obtained in the same manner as described in the above Reference Example 16.

Reference Example Compound 17-1:
1-(3-Chlorophenyl)-2-(4-pyridyl)ethanone
mp 79-80° C.

Reference Example Compound 17-2:
1-(4-Chlorophenyl)-2-(4-pyridyl)ethanone
mp 93-94° C.

Reference Example Compound 17-3:
1-(2-Methylphenyl)-2-(4-pyridyl)ethanone
oil.

^{1}H-NMR ($CDCl_3$) δ : 2.48 (3H, s), 4.23 (2H, s), 7.19 (2H, d, J= 6.2 Hz), 7.24-7.47 (3H, m), 7.73 (1H, d, J= 7.7 Hz), 8.56 (2H, d, J= 6.2 Hz).

Reference Example Compound 17-4:
1-(3-Methylphenyl)-2-(4-pyridyl)ethanone
mp 115-116° C.

Reference Example Compound 17-5:
1-(4-Methylphenyl)-2-(4-pyridyl)ethanone
mp 110-111° C.

Reference Example Compound 17-6:
1-(2-Methoxyphenyl)-2-(4-pyridyl)ethanone
oil.

^{1}H-NMR ($CDCl_3$) δ : 3.92 (3H, s), 4.30 (2H, s), 6.95-7.07 (2H, m), 7.17 (2H, d, J= 5.9 Hz), 7.50 (1H, ddd, J= 8.4, 7.3, 1.8 Hz), 7.73 (1H, dd, J= 7.7, 1.8 Hz), 8.53 (2H, d, J= 5.9 Hz).

Reference Example Compound 17-7:
1-(3-Methoxyphenyl)-2-(4-pyridyl)ethanone
oil.

^{1}H-NMR ($CDCl_3$) δ : 3.86 (3H, s), 4.28 (2H, s), 7.14 (1H, ddd, J= 8.1, 2.6, 1.1 Hz), 7.20 (2H, d, J= 6.2 Hz), 7.36 (1H, dd, J= 8.1, 7.7 Hz), 7.51 (1H, dd, J= 2.6, 1.5 Hz), 7.58 (1H, ddd, J= 7.7, 1.5, 1.1 Hz) 8.57 (2H, d, J= 6.2 Hz).

Reference Example Compound 17-8:
1-(4-Ethylphenyl)-2-(4-pyridyl)ethanone
mp 87-89° C.

Reference Example Compound 17-9:
1-[4-(1-Methylethyl)phenyl]-2-(4-pyridyl)ethanone

mp 86-88° C.

Reference Example Compound 17-10:

1-[4-(1,1-Dimethylethyl)phenyl]-2-(4-pyridyl)ethanone

mp 75-76° C.

Reference Example Compound 17-11:

1-(4-Propylphenyl)-2-(4-pyridyl)ethanone

mp 71-72° C.

Reference Example Compound 17-12:

1-(4-Butylphenyl)-2-(4-pyridyl)ethanone

mp 41-43° C.

Reference Example Compound 17-13:

1-(4-Hexylphenyl)-2-(4-pyridyl)ethanone

mp 57-58° C.

Reference Example Compound 17-14:

2-(4-Pyridyl)-1-(4-trifluoromethoxyphenyl)ethanone

mp 65-66° C.

Reference Example Compound 17-15:

2-(4-Pyridyl)-1-(4-trifluoromethylphenyl)ethanone

mp 94-95° C.

Reference Example Compound 17-16:

1-(3,4-Dimethoxyphenyl)-2-(4-pyridyl)ethanone

mp 110-111° C.

Reference Example Compound 17-17:

1-(3,4-Dimethylphenyl)-2-(4-pyridyl)ethanone

mp 81-83° C.

Reference Example Compound 17-18:

1-(3,5-Dimethylphenyl)-2-(4-pyridyl)ethanone

mp 90-91° C.

Reference Example Compound 17-19:

1-(3,4-Methylenedioxyphenyl)-2-(4-pyridyl)ethanone

mp 126-127° C.

Reference Example Compound 17-20:

1-(2-Naphthyl)-2-(4-pyridyl)ethanone

mp 114-115° C.

Reference Example 18

Using α-picoline instead of using γ-picoline, the below Reference Example Compounds 18-1 to 18-9 were obtained in the same manner as described in the above Reference Example 17.

Reference Example Compound 18-1:
1-(2-Chlorophenyl)-2-(3-pyridyl)ethanone
oil.

^{1}H-NMR ($CDCl_3$) δ : 4.28 (2H, s), 7.18-7.49 (5H, m), 7.59-7.67 (1H, m), 8.47-8.56 (2H, m).

Reference Example Compound 18-2:
1-(3-Chlorophenyl)-2-(3-pyridyl)ethanone
oil.

^{1}H-NMR ($CDCl_3$) δ : 4.29 (2H, s), 7.25-7.34 (1H, m), 7.44 (1H, t, J= 7.7 Hz), 7.54-7.63 (2H, m), 7.90 (1H, dt, J= 7.7, 1.5 Hz), 8.00 (1H, dd, J= 1.8, 1.5 Hz), 8.49-8.57 (2H, m).

Reference Example Compound 18-3:
1-(4-Chlorophenyl)-2-(3-pyridyl)ethanone

^{1}H-NMR ($CDCl_3$) δ : 4.27 (2H, s), 7.24-7.31 (1H, m), 7.47 (2H, d, J= 8.8 Hz), 7.55-7.63 (1H, m), 7.96 (2H, d, J= 8.8 Hz), 8.46-8.53 (2H, m).

Reference Example Compound 18-4:
1-(2-Methylphenyl)-2-(3-pyridyl)ethanone
oil.

^{1}H-NMR ($CDCl_3$) δ : 2.47 (3H, s), 4.23 (2H, s), 7.18-7.47 (5H, m), 7.73 (1H, d, J= 7.7 Hz), 8.47-8.56 (2H, m).

Reference Example Compound 18-5:
1-(3-Methylphenyl)-2-(3-pyridyl)ethanone
oil.

^{1}H-NMR ($CDCl_3$) δ : 2.43 (3H, s), 4.29 (2H, s), 7.17-7.36 (1H, m), 7.36-7.46 (2H, m), 7.58-7.65 (1H, m), 7.78-7.86 (2H, m), 8.50-8.56 (2H, m).

Reference Example Compound 18-6:
1-(4-Methylphenyl)-2-(3-pyridyl)ethanone
mp 72-74° C.

Reference Example Compound 18-7:
1-(3-Methoxyphenyl)-2-(3-pyridyl)ethanone
oil.
^{1}H-NMR ($CDCl_3$) δ : 3.86 (3H, s), 4.29 (2H, s), 7.14 (1H, ddd, J= 8.1, 2.6, 1.8 Hz), 7.28 (1H, dd, J= 7.3, 4.8 Hz), 7.40 (1H, dd, J= 8.1, 7.7 Hz), 7.53 (1H, dd, J= 2.6, 1.8 Hz), 7.58-7.65 (2H, m), 8.50-8.55 (2H, m).
Reference Example Compound 18-8:
1-[4-(1,1-Dimethylethyl)phenyl]-2-(3-pyridyl)ethanone
oil.
^{1}H-NMR ($CDCl_3$) δ : 1.34 (9H, s), 4.28 (2H, s), 7.22-7.31 (1H, m), 7.50 (2H, d, J= 8.4 Hz), 7.56-7.65 (1H, m), 7.96 (2H, d, J= 8.4 Hz), 8.48-8.55 (2H, m).
Reference Example Compound 18-9:
1-(3,5-Dimethylphenyl)-2-(3-pyridyl)ethanone
oil.
^{1}H-NMR ($CDCl_3$) δ : 2.38 (6H, s), 4.27 (2H, s), 7.24-7.30 (2H, m), 7.58-7.63 (3H, m), 8.50-8.52 (2H, m).

Reference Example 19

Using ethyl 4-dimethylaminobenzoate instead of using ethyl p-anisate, the below Reference Example Compound 19 was obtained in the same manner as described in the above Reference Example 1.
Reference Example Compound 19:
1-(4-Dimethylaminophenyl)-2-(4-pyridyl)ethanone
mp 189-192°C.

Reference Example 20
2-[4-(1,1-Dimethylethyl)phenyl]-1-(4-pyridyl)ethanone

To a solution of ethyl isonicotinate (12 g) and 4-(1,1-Dimethylethyl)phenylacetonitrile (9.1 g) in tert-butyl alcohol (36 mL), was added potassium tert-butoxide (7.3 g), and the mixture was stirred at 100°C for 3 h. After cooling, the resulting mixture was dissolved in water and washed with isopropyl ether. The

aqueous phase was adjusted to pH 7.0 with 2 N hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried, and the solvent was evaporated. The crystalline residue was recrystallized from ethyl acetate-isopropyl ether to obtain 2-cyano-2-[4-(1,1-dimethylethyl)phenyl]-1-(4-pyridyl)ethanone (5.09 g, yield 35 %).

2-Cyano-2-[4-(1,1-dimethylethyl)phenyl]-1-(4-pyridyl)ethanone (5.0 g) obtained above was dissolved in 48 % hydrobromic acid (50 mL) and the solution was stirred at 140° C for 5 h. After the mixture was cooled, the mixture was neutralized with an aqueous saturated solution of sodium hydrogen carbonate and the product was extracted with ethyl acetate. The extract was washed with water, dried, and the solvent was evaporated. The residue was purified using silica-gel column chromatography (hexane-ethyl acetate, 1:1) to obtain the title compound (3.1 g, yield 68 %).
oil.

^{1}H-NMR ($CDCl_3$) δ : 1.30 (9H, s), 4.25 (2H, s), 7.18 (2H, d, J= 8.4 Hz), 7.36 (2H, d, J= 8.4 Hz), 7.78 (2H, d, J= 6.2 Hz), 8.81 (2H, d, J= 6.2 Hz).

Reference Example 21

2-(3,5-Dimethylphenyl)-1-(4-pyridyl)ethanone

Using 3,5-dimethylphenylacetonitrile instead of using 4-(1,1-Dimethylethyl)phenylacetonitrile, the title compound was obtained in the same manner as described in the above Reference Example 20.
mp 96-97° C.

Reference Example 22

Using 1-(2-chlorophenyl)-2-(3-pyridyl)ethanone, 1-(3-chlorophenyl)-2-(3-pyridyl)ethanone, 1-(4-chlorophenyl)-2-(3-pyridyl)ethanone, 1-(2-methylphenyl)-2-(3-pyridyl)ethanone, 1-(3-

methylphenyl)-2-(3-pyridyl)ethanone, 1-(4-methylphenyl)-2-(3-pyridyl)ethanone, 1-(3-methoxyphenyl)-2-(3-pyridyl)ethanone, 1-[4-(1,1-dimethylethyl)phenyl]-2-(3-pyridyl)ethanone, 1-(3,5-dimethylphenyl)-2-(3-pyridyl)ethanone, 1-(2-chlorophenyl)-2-(4-pyridyl)ethanone, 1-(3-chlorophenyl)-2-(4-pyridyl)ethanone, 1-(4-chlorophenyl)-2-(4-pyridyl)ethanone, 1-(2-methylphenyl)-2-(4-pyridyl)ethanone, 1-(3-methylphenyl)-2-(4-pyridyl)ethanone, 1-(4-methylphenyl)-2-(4-pyridyl)ethanone, 1-(2-methoxyphenyl)-2-(4-pyridyl)ethanone, 1-(3-methoxyphenyl)-2-(4-pyridyl)ethanone, 1-(4-ethylphenyl)-2-(4-pyridyl)ethanone, 1-[4-(1-methylethyl)phenyl]-2-(4-pyridyl)ethanone, 1-[4-(1,1-dimethylethyl)phenyl]-2-(4-pyridyl)ethanone, 1-(4-propylphenyl)-2-(4-pyridyl)ethanone, 1-(4-butylphenyl)-2-(4-pyridyl)ethanone, 1-(4-hexylphenyl)-2-(4-pyridyl)ethanone, 2-(4-pyridyl)-1-(4-trifluoromethoxyphenyl)ethanone, 2-(4-pyridyl)-1-(4-trifluoromethylphenyl)ethanone, 1-(4-dimethylaminophenyl)-2-(4-pyridyl)ethanone hydrobromide, 1-(3,4-dimethoxyphenyl)-2-(4-pyridyl)ethanone, 1-(3,4-dimethylphenyl)-2-(4-pyridyl)ethanone, 1-(3,5-dimethylphenyl)-2-(4-pyridyl)ethanone, 1-(3,4-methylenedioxyphenyl)-2-(4-pyridyl)ethanone, 1-(2-naphthyl)-2-(4-pyridyl)ethanone, 2-[4-(1,1-dimethylethyl)phenyl]-1-(4-pyridyl)ethanone and 2-(3,5-dimethylphenyl)-1-(4-pyridyl)ethanone instead of using 1-(4-methoxyphenyl)-2-(3-pyridyl)ethanone, the below Reference Example Compounds 22-1 to 22-33 were obtained in the same manner as described in the above Reference Example 6.

Reference Example Compound 22-1:
2-Bromo-1-(2-chlorophenyl)-2-(3-pyridyl)ethanone hydrobromide

mp 88-90°C.

Reference Example Compound 22-2:

2-Bromo-1-(3-chlorophenyl)-2-(3-pyridyl)ethanone hydrobromide

mp 164-166°C.

Reference Example Compound 22-3:

2-Bromo-1-(4-chlorophenyl)-2-(3-pyridyl)ethanone hydrobromide

The crude mixture without purification was used to next reaction.

Reference Example Compound 22-4:

2-Bromo-1-(2-methylphenyl)-2-(3-pyridyl)ethanone hydrobromide

The crude mixture without purification was used to next reaction.

Reference Example Compound 22-5:

2-Bromo-1-(3-methylphenyl)-2-(3-pyridyl)ethanone hydrobromide

The crude mixture without purification was used to next reaction.

Reference Example Compound 22-6:

2-Bromo-1-(4-methylphenyl)-2-(3-pyridyl)ethanone hydrobromide

mp 96-98°C.

Reference Example Compound 22-7:

2-Bromo-1-(3-methoxyphenyl)-2-(3-pyridyl)ethanone hydrobromide

The crude mixture without purification was used to next reaction.

Reference Example Compound 22-8:

2-Bromo-1-[4-(1,1-dimethylethyl)phenyl]-2-(3-pyridyl)ethanone hydrobromide

mp 190-194°C.

Reference Example Compound 22-9:

2-Bromo-1-(3,5-dimethylphenyl)-2-(3-pyridyl)ethanone hydrobromide

mp 195-197°C.
Reference Example Compound 22-10:
2-Bromo-1-(2-chlorophenyl)-2-(4-pyridyl)ethanone hydrobromide
mp 157-159°C.
Reference Example Compound 22-11:
2-Bromo-1-(3-chlorophenyl)-2-(4-pyridyl)ethanone hydrobromide
mp 178-181°C.
Reference Example Compound 22-12:
2-Bromo-1-(4-chlorophenyl)-2-(4-pyridyl)ethanone hydrobromide
mp 189-193°C.
Reference Example Compound 22-13:
2-Bromo-1-(2-methylphenyl)-2-(4-pyridyl)ethanone hydrobromide
mp 183-186°C.
Reference Example Compound 22-14:
2-Bromo-1-(3-methylphenyl)-2-(4-pyridyl)ethanone hydrobromide
The crude mixture without purification was used to next reaction.
Reference Example Compound 22-15:
2-Bromo-1-(4-methylphenyl)-2-(4-pyridyl)ethanone hydrobromide
mp 111-113°C.
Reference Example Compound 22-16:
2-Bromo-1-(2-methoxyphenyl)-2-(4-pyridyl)ethanone hydrobromide
mp 168-171°C.
Reference Example Compound 22-17:
2-Bromo-1-(3-methoxyphenyl)-2-(4-pyridyl)ethanone hydrobromide
The crude mixture without purification was used to next reaction.
Reference Example Compound 22-18:

2-Bromo-1-(4-ethylphenyl)-2-(4-pyridyl)ethanone hydrobromide

mp 170-173° C.

Reference Example Compound 22-19:

2-Bromo-1-[4-(1-methylethyl)phenyl]-2-(4-pyridyl)ethanone hydrobromide

mp 185-188° C.

Reference Example Compound 22-20:

2-Bromo-1-[4-(1,1-dimethylethyl)phenyl]-2-(4-pyridyl)ethanone hydrobromide

mp 209-212° C.

Reference Example Compound 22-21:

2-Bromo-1-(4-propylphenyl)-2-(4-pyridyl)ethanone hydrobromide

mp 167-170° C.

Reference Example Compound 22-22:

2-Bromo-1-(4-butylphenyl)-2-(4-pyridyl)ethanone hydrobromide

mp 158-161° C.

Reference Example Compound 22-23:

2-Bromo-1-(4-hexylphenyl)-2-(4-pyridyl)ethanone hydrobromide

mp 153-155° C.

Reference Example Compound 22-24:

2-Bromo-2-(4-pyridyl)-1-(4-trifluoromethoxyphenyl)ethanone hydrobromide

The crude mixture without purification was used to next reaction.

Reference Example Compound 22-25:

2-Bromo-2-(4-pyridyl)-1-(4-trifluoromethylphenyl)ethanone hydrobromide

mp 190-194° C.

Reference Example Compound 22-26:

2-Bromo-1-(4-dimethylaminophenyl)-2-(4-pyridyl)ethanone dihydrobromide

mp 163-167° C.

Reference Example Compound 22-27:
2-Bromo-1-(3,4-dimethoxyphenyl)-2-(4-pyridyl)ethanone hydrobromide
mp 174-175° C.

Reference Example Compound 22-28:
2-Bromo-1-(3,4-dimethylphenyl)-2-(4-pyridyl)ethanone hydrobromide
mp 196-199° C.

Reference Example Compound 22-29:
2-Bromo-1-(3,5-dimethylphenyl)-2-(4-pyridyl)ethanone hydrobromide
mp 216-219° C.

Reference Example Compound 22-30:
2-Bromo-1-(3,4-methylenedioxyphenyl)-2-(4-pyridyl)ethanone hydrobromide
mp 211-214° C.

Reference Example Compound 22-31:
2-Bromo-1-(2-naphthyl)-2-(4-pyridyl)ethanone hydrobromide
mp 149-152° C.

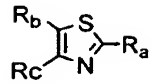
Reference Example Compound 22-32:
2-Bromo-2-[4-(1,1-dimethylethyl)phenyl]-1-(4-pyridyl)ethanone hydrobromide
The crude mixture without purification was used to next reaction.

Reference Example Compound 22-33:
2-Bromo-2-(3,5-dimethylphenyl)-1-(4-pyridyl)ethanone hydrobromide
mp 186-188° C.

Reference Example 23

The following Reference Example Compounds 23-1 to 23-222 shown in Tables 8 to 21 were obtained in the same manner as described in the above References 5 to 9, JP-A-61-10580 and USP 4,612,321.

Table 8



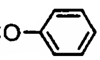
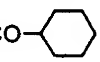
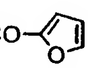
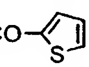
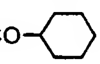
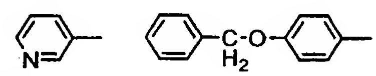
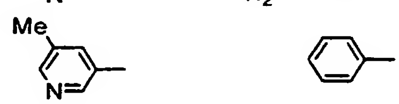
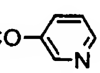
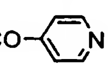
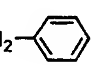
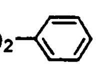
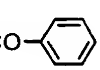
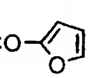
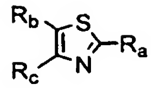
Ref. Ex. Compd.	R_a	R_b	R_c	Additive	mp / °C
23-1	-NHCO			HCl	260
23-2	-NHCO			HCl	244-246
23-3	-NHCO			HCl	255-256
23-4	-NHCO			HCl	275
23-5	-NHCO				233
23-6	-NHCOMe				218-220
23-7	-NHCOMe				218-220
23-8	-NHCO			2HCl	145-148
23-9	-NHCO				238
23-10	$-NHCOCH_2$				228-230
23-11	$-NHCO(CH_2)_2$				215-217
23-12	$-NHCO(CH_2)_2Me$				198-200
23-13	$-NHCO(CH_2)_3Me$				205-206
23-14	$-NHCO(CH_2)_4Me$				175-177
23-15	$-NHCOCMe_3$				219-220
23-16	-NHCO			HCl	268-270
23-17	-NHCO			HCl	243-246

Table 9



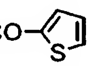
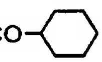
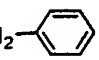
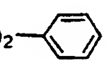
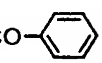
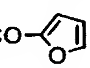
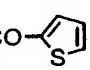
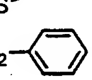
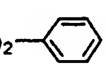
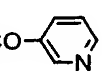
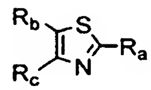
Ref. Ex. Compd.	R_a	R_b	R_c	Additive	mp / °C
23-18	-NHCO-			HCl	237-239
23-19	-NHCO-			HCl	220-223
23-20	$-NHCOCH_2-$				184-185
23-21	$-NHCO(CH_2)_2-$				214-216
23-22	$-NHCO(CH_2)_2Me$				197-198
23-23	$-NHCO(CH_2)_3Me$				188-190
23-24	$-NHCO(CH_2)_4Me$				167-169
23-25	$-NHCOCMe_3$				245-246
23-26	-NHCO-				237-238
23-27	-NHCO-				240
23-28	-NHCO-				240
23-29	$-NHCOCH_2-$				233-234
23-30	$-NHCO(CH_2)_2-$				214-216
23-31	$-NHCOCMe_3$				206-208
23-32	-NHCO-				247
23-33	$-NHCO(CH_2)_2Me$				212-214
23-34	$-NHCO(CH_2)_3Me$				232-234
23-35	$-NHCO(CH_2)_4Me$				245-246

Table 10



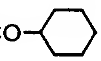
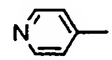
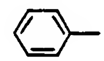
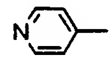
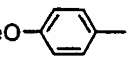
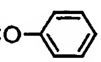
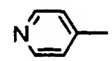
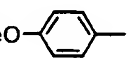
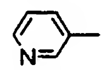
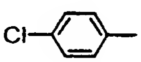
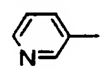
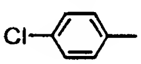
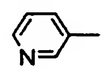
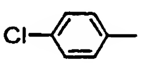
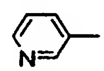
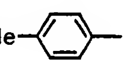
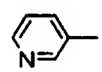
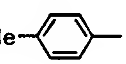
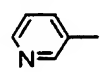
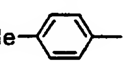
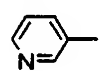
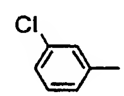
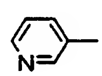
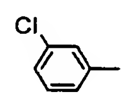
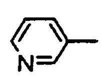
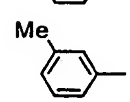
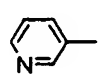
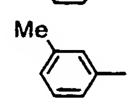
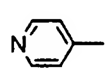
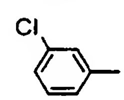
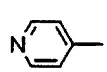
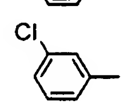
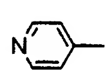
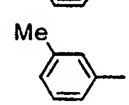
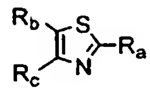
Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
23-36	-NHCO-			219-220
23-37	-NHCOCH$_2$Me		MeO-	254-256
23-38	-NHCO-		MeO-	255-257
23-39	-NH$_2$		Cl-	278-280
23-40	-NHCOMe		Cl-	266-268
23-41	-NHCOCH$_2$Me		Cl-	241-242
23-42	-NH$_2$		Me-	286-288
23-43	-NHCOMe		Me-	260-261
23-44	-NHCOCH$_2$Me		Me-	226-227
23-45	-NHCOMe			217-219
23-46	-NHCOCH$_2$Me			228-229
23-47	-NHCOMe			235-236
23-48	-NHCOCH$_2$Me			239-241
23-49	-NHCOMe			290-293
23-50	-NHCOCH$_2$Me			289-290
23-51	-NHCOMe			287-289

Table 11



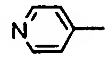
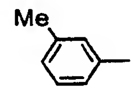
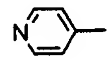
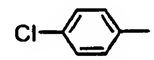
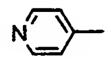
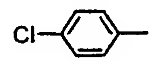
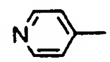
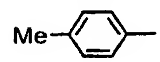
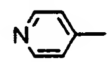
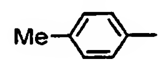
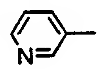
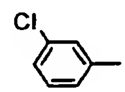
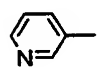
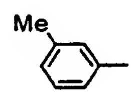
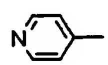
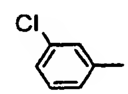
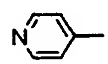
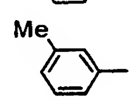
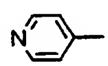
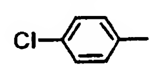
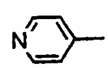
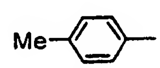
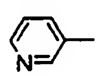
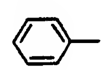
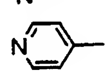
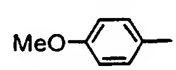
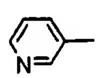
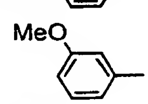
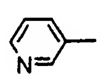
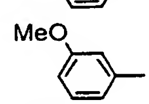
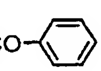
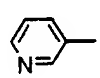
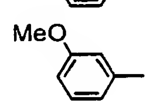
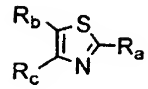
Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
23-52	-NHCOCH$_2$Me			258-260
23-53	-NHCOMe			317-320
23-54	-NHCOCH$_2$Me			257-259
23-55	-NHCOMe			308-309
23-56	-NHCOCH$_2$Me			249-250
23-57	-NH$_2$			228-230
23-58	-NH$_2$			231-232
23-59	-NH$_2$			256-258
23-60	-NH$_2$			255-258
23-61	-NH$_2$			>300
23-62	-NH$_2$			296-298
23-63	-N=C(Me)NMe$_2$			129-131
23-64	-NHCOMe			282-284
23-65	-NHCOMe			236-239
23-66	-NHCOCH$_2$Me			222-224
23-67	-NHCO 			236-239

Table 12



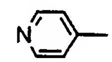
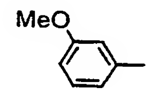
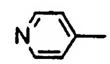
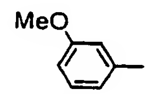
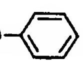
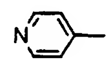
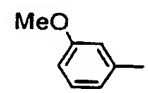
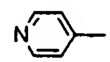
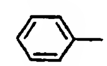
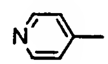
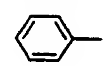
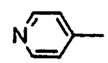
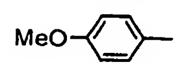
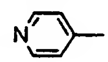
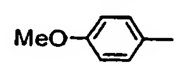
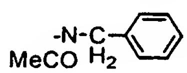
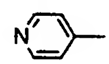
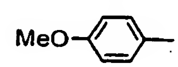
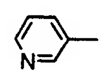
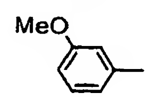
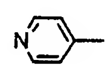
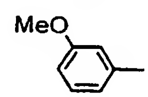
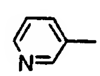
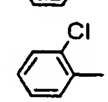
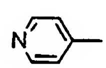
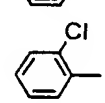
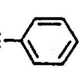
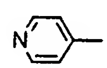
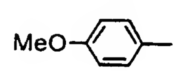
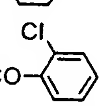
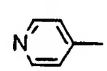
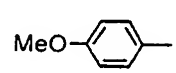
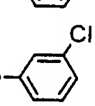
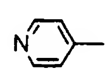
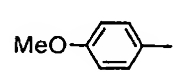
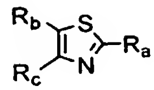
Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
23-68	-NHCOMe			234-236
23-69	$-NHCOCH_2Me$			237-239
23-70	-NHCO- 			220-222
23-71	-NHCOMe			294-297
23-72	$-NHCOCH_2Me$			267-269
23-73	$-N(CH_2Me)COMe$			143-144
23-74	$-N((CH_2)_4Me)COMe$			111-113
23-75				162-164
23-76	$-NH_2$			206-209
23-77	$-NH_2$			232-234
23-78	$-NH_2$			236-239
23-79	$-NH_2$			232-235
23-80	-NH- 			287-289
23-81	-NHCO- 			330-333
23-82	-NHCO- 			292-294

Table 13



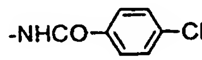
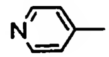
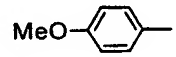
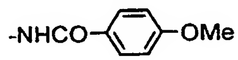
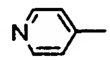
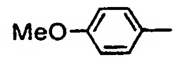
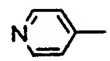
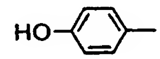
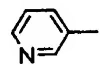
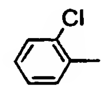
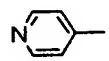
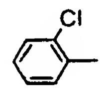
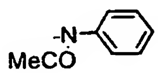
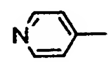
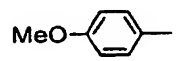
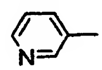
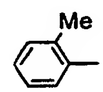
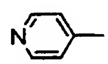
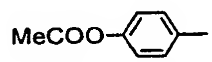
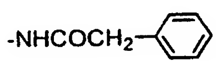
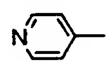
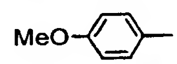
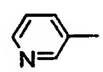
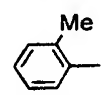
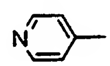
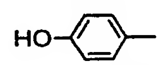
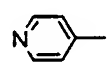
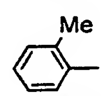
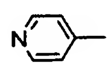
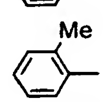
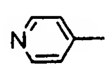
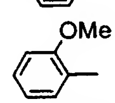
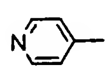
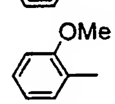
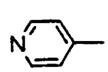
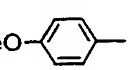
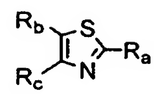
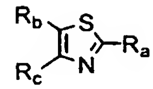
Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
23-83				346-348
23-84				308-310
23-85	-NH_2			323-326
23-86	-NHCOMe			259-261
23-87	-NHCOMe			292-293
23-88				161-163
23-89	-NH_2			235-237
23-90	-NHCOMe			254-257
23-91				274-277
23-92	-NHCOMe			237-239
23-93	-NHCOMe			285-287
23-94	-NH_2			235-238
23-95	-NHCOMe			272-274
23-96	-NH_2			213-215
23-97	-NHCOMe			259-261
23-98	-NHCO$(CH_2)_4$Cl		MeO-	228-229

Table 14



Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
23-99	-NHCOMe	4-pyridyl	C_6H_5-CH_2-O-C_6H_4-	254-257
23-100	-N(2-oxopiperidine)	4-pyridyl	MeO-C_6H_4-	159-160
23-101	-NHCO-(3-pyridyl)	4-pyridyl	MeO-C_6H_4-	278-281
23-102	-NHCO-(4-pyridyl)	4-pyridyl	MeO-C_6H_4-	295-297
23-103	-NHCO-(2-thienyl)	4-pyridyl	MeO-C_6H_4-	262-264
23-104	-NHCO-(2-furyl)	4-pyridyl	MeO-C_6H_4-	266-269
23-105	-$NHCOCHMe_2$	4-pyridyl	MeO-C_6H_4-	227-230
23-106	-$NHCOCMe_3$	4-pyridyl	MeO-C_6H_4-	254-256
23-107	-$NHCOCH_2CHMe_2$	4-pyridyl	MeO-C_6H_4-	261-262
23-108	-$NHCONH(CH_2)_2Me$	4-pyridyl	MeO-C_6H_4-	215-219
23-109	-NH_2	4-pyridyl	$MeCH_2$-C_6H_4-	285-288
23-110	-NHCOMe	4-pyridyl	$MeCH_2$-C_6H_4-	294-295
23-111	-NHCOMe	4-pyridyl	$MeCH_2O$-C_6H_4-	206-209
23-112	-NHCOMe	4-pyridyl	$Me(CH_2)_3O$-C_6H_4-	201-203
23-113	-NHCOMe	4-pyridyl	$Me(CH_2)_6O$-C_6H_4-	210-212
23-114	-$NHCO(CH_2)_3Cl$	4-pyridyl	MeO-C_6H_4-	191-194
23-115	-N(2-oxopyrrolidine)	4-pyridyl	MeO-C_6H_4-	133-135

Table 15



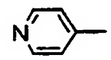
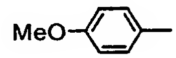
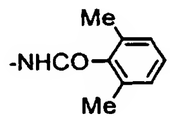
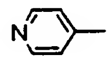
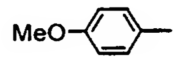
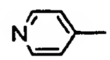
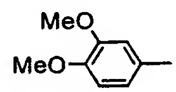
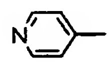
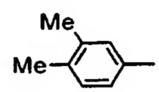
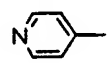
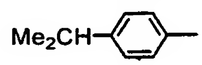
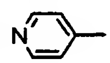
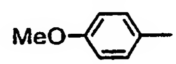
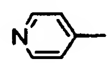
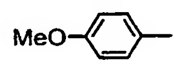
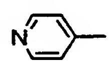
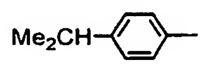
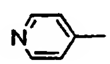
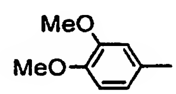
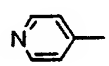
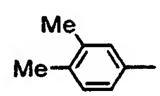
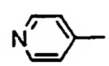
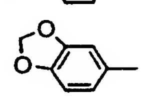
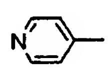
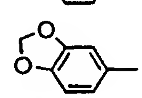
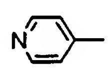
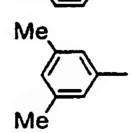
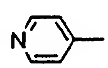
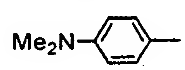
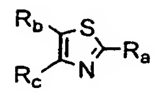
Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
23-116	$-NHCO(CH_2)_5Cl$			223-225
23-117				351-352
23-118	-NHCOMe			265-267
23-119	-NHCOMe			248-250
23-120	-NHCOMe			295-297
23-121	$-NHCO(CH_2)_2COOCH_2Me$			261-264
23-122	$-NHCO(CH_2)_2COOH$			334-336
23-123	$-NH_2$			267-269
23-124	$-NH_2$			218-219
23-125	$-NH_2$			248-250
23-126	$-NH_2$			273-275
23-127	-NHCOMe			295-296
23-128	-NHCOMe			284-286
23-129	-NHCOMe			289-291

Table 16



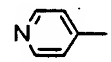
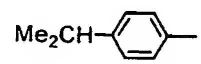
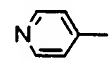
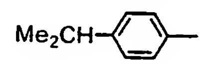
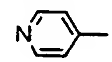
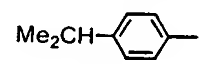
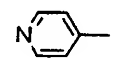
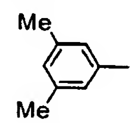
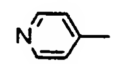
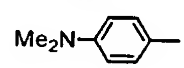
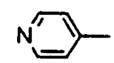
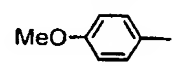
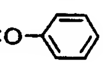
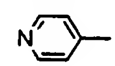
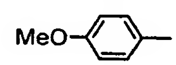
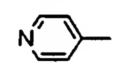
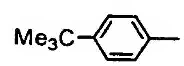
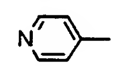
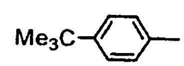
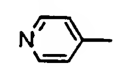
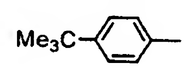
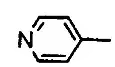
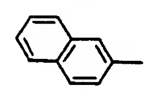
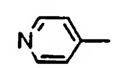
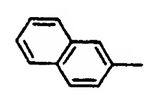
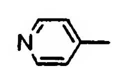
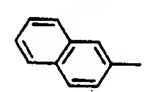
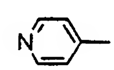
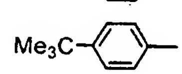
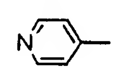
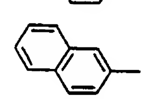
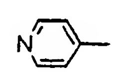
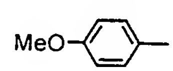
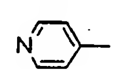
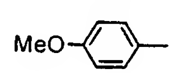
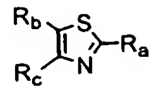
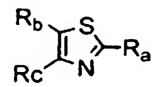
Ref. Ex. Compd.	R_a	R_b	R_c	Additive	mp / °C
23-130	-NHCOCHMe$_2$				284-285
23-131	-NHCOCMe$_3$				293-295
23-132	-NHCONH(CH$_2$)$_2$Me				287-288
23-133	-NH$_2$				242-244
23-134	-NH$_2$				309-311
23-135	-CH$_2$COOCH$_2$Me			HCl	150-152
23-136	-CH$_2$NHCO- 				150-151
23-137	-NHCOMe				280-281
23-138	-NHCOCHMe$_2$				303-304
23-139	-NHCOCMe$_3$				317-319
23-140	-NHCOMe				342-345
23-141	-NHCOCHMe$_2$				297-298
23-142	-NHCOCMe$_3$				313-315
23-143	-NH$_2$				254-257
23-144	-NH$_2$				261-264
23-145	-CH$_2$COOH				135-137
23-146	-CH$_2$CONHMe				129-130

Table 17



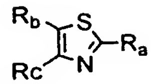
Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
23-147	-Me	N	MeO–	132-133
23-148	-NHCOMe	N	$Me(CH_2)_2$–	256-258
23-149	$-NHCOCHMe_2$	N	$Me(CH_2)_2$–	269-272
23-150	-NHCO–	N	$Me(CH_2)_2$–	240-242
23-151	-NHCOMe	N	$Me(CH_2)_3$–	259-261
23-152	-NHCOMe	N	$Me(CH_2)_5$–	237-239
23-153	-NHCOMe	N	CF_3O–	296-298
23-154	$-NHCOCHMe_2$	N	CF_3O–	285-286
23-155	$-NHCOCF_3$	N	MeO–	260-262
23-156	$-NHCONHCH_2Me$	N	MeO–	224-226
23-157	$-NHCONHCH_2Me$	N	Me_2CH–	181-183
23-158	$-NH_2$	N	$Me(CH_2)_2$–	240-242
23-159	$-NH_2$	N	$Me(CH_2)_3$–	204-206
23-160	$-NH_2$	N	$Me(CH_2)_5$–	178-179
23-161	$-NH_2$	N	CF_3O–	262-264
23-162	-COOH	N	MeO–	141-143
23-163	$-NHCOCH_2Me$	N	Me_3C–	295-297
23-164	-NHCO–	N	Me_3C–	292-294
23-165	-NHCO– (N)	N	Me_3C–	326-328

Table 18



Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
23-166	-NHCO- N	N	Me_3C-	326-329
23-167	$-NHCOCH_2-$	N	Me_3C-	277-279
23-168	-NHCO-	N	Me_3C-	309-311
23-169	$-NHCONHCH_2Me$	N	Me_3C-	289-292
23-170	$-NHCONH(CH_2)_2Me$	N	Me_3C-	212-214
23-171	$-NHCOCH_2OMe$	N	Me_3C-	248-249
23-172	-NHCOMe	N	Me_3C-	228-230
23-173	$-NHCOCH_2Me$	N	Me_3C-	244-246
23-174	$-NHCOCHMe_2$	N	Me_3C-	228-229
23-175	$-NHCOCH_2-$	N	Me_3C-	204-206
23-176	-NHCO-	N	Me_3C-	216-218
23-177	-NHCO-	N	Me_3C-	218-220
23-178	-NHCO- N	N	Me_3C-	251-253
23-179	-NHCO- N	N	Me_3C-	271-273
23-180	$-NHCONHCH_2Me$	N	Me_3C-	302-305
23-181	$-NHCONH(CH_2)_2Me$	N	Me_3C-	190-192
23-182	$-NH_2$	N	Me_3C-	239-241
23-183	$-NH_2$	N	CF_3-	304-306

Table 19



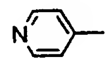
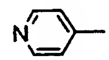
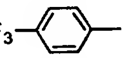
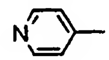
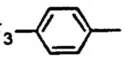
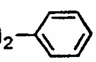
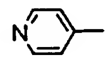
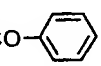
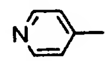
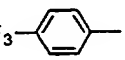
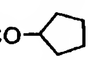
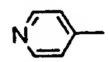
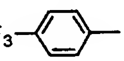
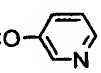
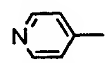
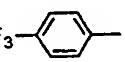
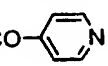
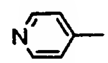
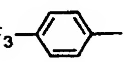
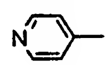
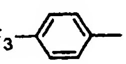
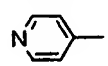
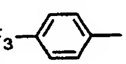
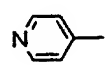
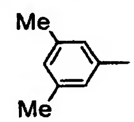
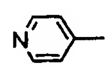
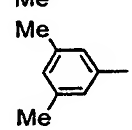
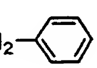
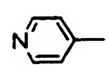
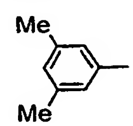
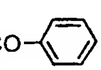
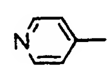
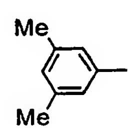
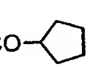
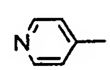
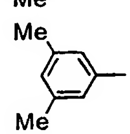
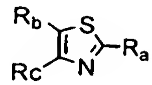
Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
23-184	-NHCOMe		CF_3– 	328-330
23-185	-NHCOCH$_2$Me		CF_3– 	284-286
23-186	-NHCOCHMe$_2$		CF_3– 	274-275
23-187	-NHCOCH$_2$– 		CF_3– 	295-296
23-188	-NHCO– 		CF_3– 	254-255
23-189	-NHCO– 		CF_3– 	272-273
23-190	-NHCO– 		CF_3– 	262-264
23-191	-NHCO– 		CF_3– 	263-264
23-192	-NHCONHCH$_2$Me		CF_3– 	206-207
23-193	-NHCONH(CH$_2$)$_2$Me		CF_3– 	208-210
23-194	-NHCOCH$_2$Me			291-293
23-195	-NHCOCHMe$_2$			270-272
23-196	-NHCOCH$_2$– 			226-229
23-197	-NHCO– 			285-286
23-198	-NHCO– 			275-278

Table 20



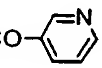
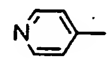
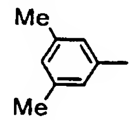
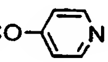
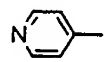
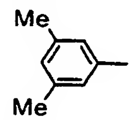
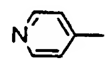
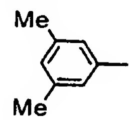
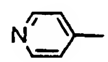
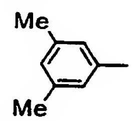
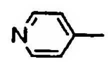
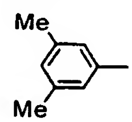
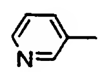
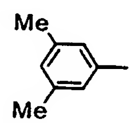
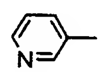
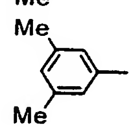
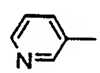
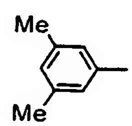
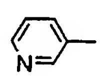
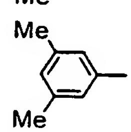
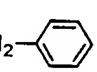
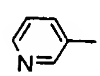
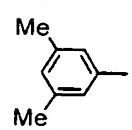
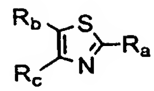
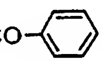
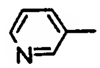
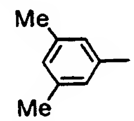
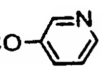
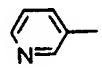
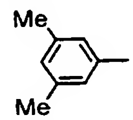
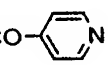
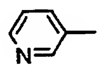
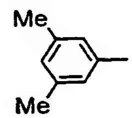
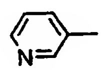
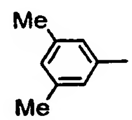
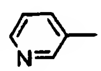
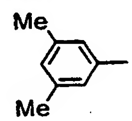
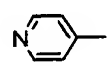
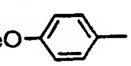
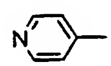
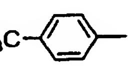
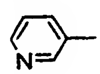
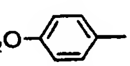
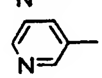
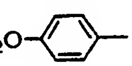
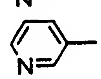
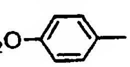
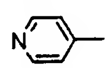
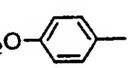
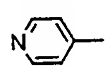
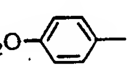
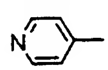
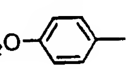
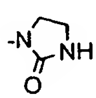
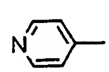
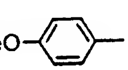
Ref. Ex. Compd.	R_a	R_b	R_c	mp / °C
23-199	-NHCO- 			267-270
23-200	-NHCO- 			302-304
23-201	$-NHCONHCH_2Me$			202-203
23-202	$-NHCONH(CH_2)_2Me$			128-130
23-203	$-NHCOCH_2OMe$			220-222
23-204	$-NH_2$			237-240
23-205	-NHCOMe			288-289
23-206	$-NHCOCH_2Me$			292-293
23-207	$-NHCOCHMe_2$			253-254
23-208	$-NHCOCH_2-$ 			235-238

Table 21



Ref. Ex. Compd.	R_a	R_b	R_c	Additive	mp / °C
23-209	-NHCO-				300-301
23-210	-NHCO-				277-278
23-211	-NHCO-				278-280
23-212	-NHCONHCH$_2$Me				220-224
23-213	-NHCONH(CH$_2$)$_2$Me				204-206
23-214	-COOCH$_2$Me		MeO-		149-150
23-215	-NHCOCH$_2$NMe$_2$		Me$_3$C-		230-231
23-216	-NH$_2$		MeCH$_2$OCOCH$_2$O-		167-169
23-217	-NHCOMe		MeCH$_2$OCOCH$_2$O-		195-197
23-218	-NHCOMe		HOCOCH$_2$O-		266-270
23-219	-NH$_2$		MeCH$_2$OCOCH$_2$O-		181-185
23-220	-NHCOMe		MeCH$_2$OCOCH$_2$O-		239-244
23-221	-NHCOMe		HOCOCH$_2$O-	HCl	237-242
23-222			MeO-		248-250

Example 1

N-Methyl[5-phenyl-4-(3-pyridyl)-1,3-thiazol-2-yl]amine

To a solution of N-methylthiourea (484 mg) in acetonitrile (40 mL), was added 2-bromo-2-phenyl-1-(3-pyridyl)ethanone hydrobromide (2.0 g), and then triethylamine (0.8 mL) was added dropwise to the mixture with stirring. After addition, the resulting mixture was stirred at reflux for 3 h and the solvent was evaporated. An aqueous saturated solution of sodium hydrogen carbonate was added to the residue and extracted with ethyl acetate. The extracts were washed with water, dried and the solvent was evaporated. The crystalline residue was recrystallized from ethyl acetate-isopropyl ether to give the title compound (1.2 g, yield 80 %).

mp 144-145°C.

Example 2

[5-Phenyl-4-(3-pyridyl)-1,3-thiazol-2-yl]amine

To a mixture of 2-bromo-2-phenyl-1-(3-pyridyl)ethanone hydrobromide (2.00 g) and thiourea (432 mg) in acetonitrile (30 mL), was added triethylamine (0.80 mL) dropwise and the resulting mixture was stirred at 80°C for 3 h. The solvent was removed under reduced pressure and an aqueous saturated solution of sodium hydrogen carbonate was added to the residue. The mixture was extracted with ethyl acetate. The organic phases were washed with water, dried and concentrated under reduced pressure to give the amorphous title compound (1.10 g, yield 84 %).

^{1}H-NMR ($CDCl_3$) δ : 5.31 (2H, br s), 7.13-7.29 (6H, m), 7.76 (1H, dt, J = 7.8, 1.8 Hz), 8.46 (1H, dd, J = 5.0, 1.8 Hz), 8.70 (1H, d, J = 1.8 Hz).

Example 3

N-[5-Phenyl-4-(3-pyridyl)-1,3-thiazol-2-yl]acetamide

To a solution of [5-phenyl-4-(3-pyridyl)-1,3-thiazol-2-yl]amine (1.10 g, 4.34 mmol) in N,N-dimethylacetamide (20 mL) was added acetyl chloride (680 mg, 8.68 mmol) and stirred at 80°C for 3 h. Water was added to the reaction mixture and extracted with ethyl acetate twice. The combined organic phases were washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from chloroform-ethyl ether to give the title compound (750 mg, yield 59 %).
mp 264-267°C.

Example 4

Using 2-bromo-2-[4-(1,1-dimethylethyl)phenyl]-1-(4-pyridyl)ethanone hydrobromide and 2-bromo-2-(3,5-dimethylphenyl)-1-(4-pyridyl)ethanone hydrobromide instead of using 2-bromo-2-phenyl-1-(3-pyridyl)ethanone hydrobromide, the below Example Compounds 4-1 and 4-2 were obtained in the same manner as described in above Example 2.

Example Compound 4-1:
[5-[4-(1,1-dimethylethyl)phenyl]-4-(4-pyridyl)-1,3-thiazol-2-yl]amine
mp 275-277°C.

Example Compound 4-2:
[5-(3,5-dimethylphenyl)-4-(4-pyridyl)-1,3-thiazol-2-yl]amine
mp 262-263°C.

Example 5

Using [5-[4-(1,1-dimethylethyl)phenyl]-4-(4-pyridyl)-1,3-thiazol-2-yl]amine and [5-(3,5-dimethylphenyl)-4-(4-pyridyl)-1,3-thiazol-2-yl]amine instead of using [5-phenyl-4-(3-pyridyl)-1,3-thiazol-2-yl]amine, the below Example Compounds 5-1 and 5-2 were obtained in the same manner as described in above

Example 3.

Example Compound 5-1:

N-[5-[4-(1,1-dimethylethyl)phenyl]-4-(4-pyridyl)-1,3-thiazol-2-yl]acetamide

mp 245-246°C.

Example Compound 5-2:

N-[5-(3,5-dimethylphenyl)-4-(4-pyridyl)-1,3-thiazol-2-yl]acetamide

mp 304-308°C.

Example 6

2-Ethyl-5-phenyl-4-(3-pyridyl)-1,3-thiazole

Using propanethioamide instead of using N-methylthiourea, the title compound was obtained in the same manner as described in the above Example 1.

mp 144-145°C

Example 7

4-[5-Phenyl-4-(3-pyridyl)-1,3-thiazol-2-yl]butyric acid

A solution of methyl 4-[5-phenyl-4-(3-pyridyl)-1,3-thiazol-2-yl]butyrate (4.1 g), which was obtained in the same manner as described in the above Example 1 using 4-(methoxycarbonyl)butanethioamide instead of using N-methylthiourea, in methanol (15 mL) was added to an 8N aqueous sodium hydroxide solution (20 mL) and stirred at 80°C for 2h. The mixture was adjusted to pH 6.0 with 2N hydrochloric acid and the product was extracted with ethyl acetate. The extract was washed with water, dried and the solvent was evaporate. The residue was recrystallized from ethyl acetate to afford the title compound (3.4 g, yield 87 %).

mp 141-142°C

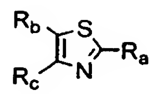
Example 8

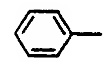
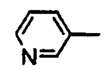
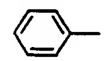
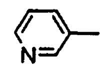
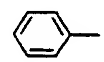
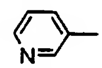
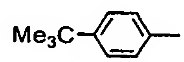
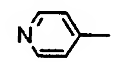
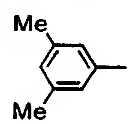
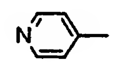
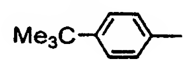
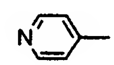
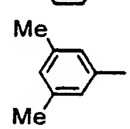
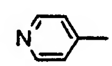
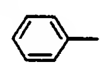
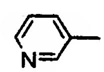
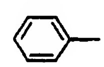
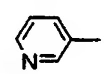
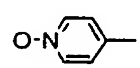
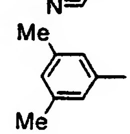
4-[2-Acetylamino-4-(3,5-dimethylphenyl)-1,3-thiazol-5-yl]pyridine 1-oxide

To a suspension of N-[4-(3,5-dimethylphenyl)-5-(4-pyridyl)-1,3-thiazol-2-yl]acetamide (1.0 g) in chloroform (30 mL), was added 70% m-chloroperbenzoic acid (0.80 g), and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the residue was treated with an aqueous saturated solution of sodium hydrogen carbonate. The formed crystalline residue was washed with water, dried and recrystallized from ethanol to obtain the title compound (0.55 g, yield 53 %).
mp 332-334° C

The chemical structures obtained in Examples 1 to 8 are shown in Table 22.

Table 22



Ex. Compd.	R_a	R_b	R_c
1	-NHMe		
2	$-NH_2$		
3	-NHCOMe		
4-1	$-NH_2$		
4-2	$-NH_2$		
5-1	-NHCOMe		
5-2	-NHCOMe		
6	$-CH_2Me$		
7	$-(CH_2)_3COOH$		
8	-NHCOMe		

Formulation Example 1

(1)	Reference Example Compound 13-89	50 mg
(2)	Lactose	34 mg
(3)	Corn starch	10.6 mg
(4)	Corn starch (paste)	5 mg
(5)	Magnesium stearate	0.4 mg
(6)	Calcium carboxymethyl cellulose	20 mg
	Total	120 mg

(1) to (6) were mixed in an ordinary manner, and tabletted into tablets using a tabletting machine.

Experimental Example 1

The following procedures in this Example were carried out according to the methods described in Molecular Cloning - Cold Spring Harbor Laboratory (1989) or protocol specified by manufacturers.

(1) Cloning of human adenosine A_3 receptor

Cloning of the human adenosine A_3 receptor gene was carried out by the polymerase chain reaction (PCR) from human brain cDNA. Using 1 ng of brain cDNA (Quick-Clone cDNA, TOYOBO, Osaka) as template, PCR was performed in DNA Thermal Cycler 480 (Perkin Elmer, Foster, CA) (reaction conditions: 35 cycles of 1 min at 95 °C, 1 min at 66 °C, and 2 min at 75 °C) by mixing primers (50 pmol each), 5'-CGCCTCTAGACAAGATGCCCAACAACAGCACTGC-3' [Sequence No. 1] and 5'-CGGGGTCGACACTACTCAGAATTCTTCTCAATGC-3' [Sequence No. 2], which were designed referring to nucleotide sequence of adenosine A_3 receptor gene reported by Salvatore et. al., (Proc. Natl. Acad. Sci. U. S. A., 90:10365-10369, 1993) and TaKaRa LA PCR Kit Ver.2 (TaKaRa Shuzo Co. Ltd., Kyoto) in a Thermal cycler 480 (Parkin Elmer). The PCR product was electrophoresed and 1.0 kb DNA fragment was recovered. The DNA fragment encoding adenosine A_3 receptor was cloned using Original TA Cloning Kit (FUNAKOSHI, Tokyo).

Thus obtained plasmid was digested with *Xba* I (TaKaRa Shuzo Co. Ltd., Kyoto), blunted with T4 DNA polymerase (TaKaRa Shuzo Co. Ltd., Kyoto) and digested with *Sal* I (TaKaRa Shuzo Co. Ltd., Kyoto) to obtain adenosine A_3 receptor gene fragment.

(2) Construction of human adenosine A_3 receptor expression plasmid

The SRα promoter from pTB1411 disclosed in JP-A-5-076385 was ligated into the pCI vector (Promega, Tokyo), which was digested with *Bgl* II (TaKaRa Shuzo Co. Ltd., Kyoto), blunted and digested with *Eco*RI (TaKaRa Shuzo Co. Ltd., Kyoto) subsequently. The resulting plasmid, designated as pCI-SRα, was then digested with *Cla* I (TaKaRa Shuzo Co. Ltd., Kyoto) and blunted with T4 DNA polymerase (TaKaRa Shuzo Co. Ltd., Kyoto). On the other hand, pGFP-C1 (TOYOBO, Osaka) was digested with *Bsu* 36I (DAIICHIKAGAKUYAKUHIN, Tokyo) and the 1.63kb fragment was recovered after the blunting with T4 DNA polymerase to ligate to the pCI-SRα vector using DNA Ligation kit (TaKaRa Shuzo Co. Ltd., Kyoto). The ligation mixture was used to transform *E.coli* JM109 competent cells (TaKaRa Shuzo Co. Ltd., Kyoto). The resulting plasmid thus obtained was designated as pMSRαneo.

pMSRαneo was digested with *Eco*RI (TaKaRa Shuzo Co. Ltd., Kyoto), blunted with T4 DNA polymerase (TaKaRa Shuzo Co. Ltd., Kyoto) and then digested with *Sal* I (TaKaRa Shuzo Co. Ltd., Kyoto). After the reaction mixture was fractionated on agarose gel, the DNA at size of 5.4 kb was ligated with adenosine A_3 receptor obtained in the above (1) by using DNA Ligation kit (TaKaRa Shuzo Co. Ltd., Kyoto). The ligation mixture was used to transform E.coli JM109 competent cells (TaKaRa Shuzo Co. Ltd., Kyoto). The plasmid thus obtained was designated as pA3SRα.

(3) Transfection of adenosine A_3 receptor expression plasmid into CHO ($dhfr^-$) and the expression

CHO ($dhfr^-$) cells were grown on Ham's F-12 medium (Nihon Seiyaku, Tokyo) supplement with 10 % fetal bovine serum (Life Tech Oriental; Life Technologies, Inc., Rockville, MD, USA) in a 750 ml Tissue culture flask (Becton Dickinson, Mt. View, CA). The growing

cells were treated with 0.5g/l trypsin-0.2g/l EDTA (Life Technologies, Inc., Rockville, MD, USA) to harvest, washed with PBS (Life Technologies, Inc., Rockville, MD, USA), centrifugated at 1000 rpm for 5 min, and suspended in PBS. Transfection with pA3SRα into the cell was performed by electroporation using a Bio-Rad/Gene Pulser (Bio-Rad, Tokyo) at 0.25 V/960 μF (8×10^6 cells/10 μg DNA/0.4 cm electrode gap cuvette). The transfected cells were transferred into Ham's F-12 medium containing 10 % fetal bovine serum, cultivated for 24 hours, harvested, suspended in Ham's F-12 media supplement with 10 % fetal bovine serum and 500 μg/ml geneticin (Life Technologies Inc., Rockville, MD, USA) at a cell density of 10^4 cells/ml. The cells were plated onto 96 well plates (Becton Dickinson, Mt. View, CA) containing Ham's F-12 media supplement with 10 % fetal bovine serum and 500 μg/ml geneticin (Life Technologies Inc., Rockville, MD, USA) at a cell density of 10^4 cells/ml. The geneticin resistant cells thus obtained were further cultivated on 24 well plates (Becton Dickinson, Mt. View, CA) and the cells expressing adenosine A_3 receptor were selected from them as follows. The cells were incubated in assay buffer I (HBSS (Wako chemicals, Osaka) containing 0.1 % BSA, 0.25 mM PMSF, 1 μg/ml pepstatin, and 20 μg/ml leupeptin) to which was added 50 pM ^{125}I-AB-MECA (Amersham) as ligand, for 1 hour, and washed with assay buffer I. The radioactivity associated with the cell was measured in a γ-counter to select A3AR/CHO cells which specifically bind to the ligand.

(4) Cell membrane preparation of the transfectant expressing adenosine A_3 receptor

After A3AR/CHO cells obtained in the above (3) were cultivated in Ham's F-12 medium containing 10 %

fetal bovine serum for 2 days, the cells were treated with PBS plus 0.02% EDTA, centrifuged to collect, resuspended in assay buffer II (50 mM Tris-HCl (pH7.5), 1 mM EDTA, 10 mM $MgCl_2$, 0.25 mM PMSF, 1 μg/ml pepstatin, and 20 μg/ml leupeptin) and homogenized using Polytron homogenizer (PT-3000, KINEMATICA AG: 20,000 rpm, 20 sec, 3 times). This suspension was centrifuged at 2,000 rpm for 10 min and supernatant fraction containing cell membranes was obtained. The supernatant fraction was ultra-centrifuged at 30,000 rpm (model L8-70M, rotor 70Ti, Beckman) for 1 hour. Thus obtained pellet was resuspended in assay buffer II containing 2 unit/ml adenosine deaminase (Boehriger Mannheim, Tokyo) and incubated at 30 °C for 30 min. The suspension was ultra-centrifuged under the same condition as above and the cell membrane fraction was obtained as the pellet.

(5) Binding assays with adenosine A_3 receptor

10 nM of [^{3}H]-NECA (Amersham Life Sciences, Inc., Tokyo) as ligand was added to the reaction mixture including test compound at various concentration and 100 μg/ml of membranes obtained in (4) in assay buffer II. The reaction mixture was incubated for 1 hour at room temperature and filtrated through the Unifilter GF/C (Packard Instrument Company, Tokyo) to transfer the membrane onto the filter, using Cell Harvester (Packard Instrument Company, Tokyo). The filter was washed three times with ice-cold 50 mM Tris-HCl (pH 7.5), and dried. Then, Microscint-0 was placed on the filter and radioactivity retained on the filter was determined by Top-Count (Packard Instrument Company, Tokyo). Curve-fit and the concentration that inhibits 50 % specific binding (IC_{50}) to the membrane of [^{3}H]-NECA were calculated by program Prizm 2.01 (Graph Pad Software, San Diego).

Results are shown in Table 23.

Table 23

Reference Compound No.	IC_{50} (nM)
10	0.27
13-89	0.55
13-92	0.70

This result shows that the compound (I) has a high affinity for adenosine A_3 receptor.

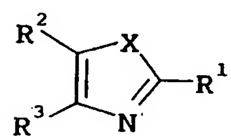
INDUSTRIAL APPLICABILITY

Since compound (I) containing compounds (Ia), (Ib) and (Ic) has a potent A_3 adenosine receptor antagonistic activity and low toxicity, it is useful as A_3 adenosine receptor antagonist and can be used as a prophylactic and therapeutic agent for asthma, allergosis, inflammation, Addison's diseases, autoallergic hemolytic anemia, Crohn's diseases, psoriasis, rheumatism, diabetes and so on.

CLAIMS

1. A pharmaceutical composition for antagonizing adenosine at adenosine A_3 receptors which comprises a 1,3-azole compound substituted on the 4- or 5-position, or both, by a pyridyl which may be substituted.

2. A composition of claim 1, wherein the 1,3-azole compound is a compound of the formula:



wherein R^1 represents a hydrogen atom, a hydrocarbon group which may be substituted, a heterocyclic group which may be substituted, an amino which may be substituted or an acyl;

at least one of R^2 and R^3 represents a hydrogen atom, a pyridyl which may be substituted or an aromatic hydrocarbon group which may be substituted, and the other represents a pyridyl which may be substituted; and

X represents a sulfur atom which may be oxidized, an oxygen atom or a group of the formula: NR^4 wherein R^4 represents a hydrogen atom, a hydrocarbon group which may be substituted or an acyl;

or a salt thereof, which may be N-oxidized.

3. A composition of claim 2, wherein R^1 is (i) a hydrogen atom,

(ii) a C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-14} aryl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents,

(iii) a 5- to 14-membered heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, which group may be substituted by 1 to 5

substituents,
(iv) an amino which may be substituted by 1 or 2 substituents selected from the group consisting of
(a) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-14} aryl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents,
(b) a C_{1-6} alkylidene group which may be substituted by 1 to 5 substituents,
(c) a 5- to 14-membered heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents, and
(d) an acyl of the formula: $-(C=O)-R^5$, $-(C=O)-OR^5$, $-(C=O)-NR^5R^6$, $-(C=S)-NHR^5$ or $-SO_2-R^7$ wherein R^5 is (i') a hydrogen atom, (ii') a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-14} aryl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents or (iii') a 5- to 14-membered heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents; R^6 is a hydrogen atom or C_{1-6} alkyl; and R^7 is (i') a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-14} aryl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents or (ii') a 5- to 14-membered heterocyclic group containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms, which group may be substituted by 1 to 5 substituents,

(v) a 5- to 7-membered non-aromatic cyclic amino optionally containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms and at least one nitrogen atom, which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl, C_{6-14} aryl, C_{1-6} alkyl-carbonyl, 5- to 10-membered aromatic heterocyclic group and oxo, or
(vi) an acyl of the formula: $-(C=O)-R^5$, $-(C=O)-OR^5$, $-(C=O)-NR^5R^6$, $-(C=S)-NHR^5$ or $-SO_2-R^7$ wherein each symbol is as defined above;
at least one of R^2 and R^3 is (i) a hydrogen atom, (ii) a pyridyl which may be substituted by 1 to 5 substituents or
(iii) a C_{6-14} aryl which may be substituted by 1 to 5 substituents in which a substituent can form, together with a neighboring substituent, a 4- to 7-membered non-aromatic carbocyclic ring;
and the other is a pyridyl which may be substituted by 1 to 5 substituents; and
X is a sulfur atom which may be oxidized, an oxygen atom or a group of the formula: NR^4 wherein R^4 is (i) a hydrogen atom, (ii) a C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-14} aryl or C_{7-16} aralkyl group which may be substituted by 1 to 5 substituents or (iii) an acyl of the formula: $-(C=O)-R^5$, $-(C=O)-OR^5$, $-(C=O)-NR^5R^6$, $-(C=S)-NHR^5$ or $-SO_2-R^7$ wherein each symbol is as defined above,
wherein the above "substituents" are selected from the group consisting of (1) halogen atoms, (2) C_{1-3} alkylenedioxy, (3) nitro, (4) cyano, (5) optionally halogenated C_{1-6} alkyl, (6) optionally halogenated C_{2-6} alkenyl, (7) carboxy C_{2-6} alkenyl, (8) optionally

halogenated C_{2-6} alkynyl, (9) optionally halogenated C_{3-6} cycloalkyl, (10) C_{6-14} aryl, (11) optionally halogenated C_{1-8} alkoxy, (12) C_{1-6} alkoxy-carbonyl-C_{1-6} alkoxy, (13) hydroxy, (14) C_{6-14} aryloxy, (15) C_{7-16} aralkyloxy, (16) mercapto, (17) optionally halogenated C_{1-6} alkylthio, (18) C_{6-14} arylthio, (19) C_{7-16} aralkylthio, (20) amino, (21) mono-C_{1-6} alkylamino, (22) mono-C_{6-14} arylamino, (23) di-C_{1-6} alkylamino, (24) di-C_{6-14} arylamino, (25) formyl, (26) carboxy, (27) C_{1-6} alkyl-carbonyl, (28) C_{3-6} cycloalkyl-carbonyl, (29) C_{1-6} alkoxy-carbonyl, (30) C_{6-14} aryl-carbonyl, (31) C_{7-16} aralkyl-carbonyl, (32) C_{6-14} aryloxy-carbonyl, (33) C_{7-16} aralkyloxy-carbonyl, (34) 5- or 6-membered heterocycle carbonyl, (35) carbamoyl, (36) mono-C_{1-6} alkyl-carbamoyl, (37) di-C_{1-6} alkyl-carbamoyl, (38) C_{6-14} aryl-carbamoyl, (39) 5- or 6-membered heterocycle carbamoyl, (40) C_{1-6} alkylsulfonyl, (41) C_{6-14} arylsulfonyl, (42) formylamino, (43) C_{1-6} alkyl-carbonylamino, (44) C_{6-14} aryl-carbonylamino, (45) C_{1-6} alkoxy-carbonylamino, (46) C_{1-6} alkylsulfonylamino, (47) C_{6-14} arylsulfonylamino, (48) C_{1-6} alkyl-carbonyloxy, (49) C_{6-14} aryl-carbonyloxy, (50) C_{1-6} alkoxy-carbonyloxy, (51) mono-C_{1-6} alkyl-carbamoyloxy, (52) di-C_{1-6} alkyl-carbamoyloxy, (53) C_{6-14} aryl-carbamoyloxy, (54) nicotinoyloxy, (55) 5- to 7-membered saturated cyclic amino which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl, C_{6-14} aryl, C_{1-6} alkyl-carbonyl, 5- to 10-membered aromatic heterocyclic group and oxo, (56) 5- to 10-membered aromatic heterocyclic group and (57) sulfo.

4. A composition of claim 2, wherein R^1 is an amino which may be substituted.

5. A composition of claim 3, wherein R^1 is an amino which may be substituted by 1 or 2 acyl of the formula: $-(C=O)-R^5$, $-(C=O)-OR^5$, $-(C=O)-NR^5R^6$, $-(C=S)-NHR^5$ or $-SO_2-R^7$.

6. A composition of claim 3, wherein R^1 is an amino which may be substituted by 1 or 2 acyl of the formula: $-(C=O)-R^5$ or $-(C=O)-NR^5R^6$.

7. A composition of claim 3, wherein R^1 is a 5- to 7-membered non-aromatic cyclic amino optionally containing 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur and oxygen atoms in addition to carbon atoms and at least one nitrogen atom, which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-6} alkyl, C_{6-14} aryl, C_{1-6} alkyl-carbonyl, 5- to 10-membered aromatic heterocyclic group and oxo.

8. A composition of claim 2, wherein X is S.

9. A composition of claim 2, wherein R^2 is a pyridyl which may be substituted.

10. A composition of claim 2, wherein R^3 is a C_{6-14} aryl which may be substituted.

11. A composition of claim 3, wherein R^1 is an amino which may be substituted by 1 or 2 acyl of the formula: $-(C=O)-R^5$ or $-(C=O)-NR^5R^6$;

R^2 is a pyridyl which may be substituted by 1 to 5 C_{1-6} alkyl;

R^3 is a C_{6-14} aryl which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy and carboxy; and

X is S.

12. A composition of claim 2, wherein R^1 is (i) a C_{1-8} alkyl, C_{3-6} cycloalkyl or C_{6-10} aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of halogen atoms, optionally halogenated C_{1-6} alkyl, carboxy C_{2-6} alkenyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkoxy-carbonyl-C_{1-6} alkoxy, hydroxy, amino, mono-C_{1-6} alkylamino, carboxy, C_{1-6} alkoxy-carbonyl, mono-C_{1-6} alkyl-carbamoyl and C_{6-14} aryl-carbonylamino,

(ii) a 5-membered heterocyclic group,

(iii) an amino which may be substituted by 1 or 2 substituents selected from the group consisting of (1) C_{1-6} alkyl,(2) C_{6-14} aryl, (3) C_{7-16} aralkyl, (4) 6-membered heterocyclic group, (5) a C_{1-6} alkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl, C_{6-14} aryl-carbonyl, C_{7-16} aralkyl-carbonyl, C_{1-6} alkyl-carbamoyl or 5- or 6-membered heterocycle carbonyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl, C_{1-6} alkoxy, carboxy and C_{1-6} alkoxy-carbonyl, and (6) di-C_{1-6} alkylamino-C_{1-6} alkylidene,

(iv) a 5- or 6-membered non-aromatic cyclic amino which may be substituted by C_{1-6} alkyl-carbonyl or oxo, or

(v) carboxy;

R^2 is a pyridyl which may be substituted by 1 to 3 C_{1-6} alkyl;

R^3 is a C_{6-10} aryl which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms, C_{1-3} alkylenedioxy, optionally halogenated C_{1-6} alkyl, carboxy C_{2-6} alkenyl,

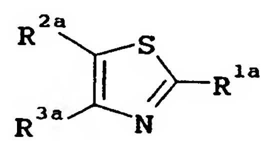
optionally halogenated C_{1-8} alkoxy, hydroxy, C_{7-16} aralkyloxy and C_{1-6} alkyl-carbonyloxy, in which the alkyl group can form, together with a neighboring alkyl group, a 5-membered non-aromatic carbocyclic ring; and

X is S.

13. An adenosine A_3 receptor antagonist which comprises a 1,3-azole compound substituted on the 4- or 5-position, or both, by a pyridyl which may be substituted.

14. A composition of claim 1, which is for preventing and/or treating asthma or allergosis.

15. A compound of the formula:



wherein R^{1a} represents (i) an aromatic heterocyclic group which may be substituted, (ii) an amino which may be substituted by substituent(s) selected from the group consisting of a substituted carbonyl and a hydrocarbon group which may be substituted, (iii) a cyclic amino which may be substituted or (iv) an acyl;

R^{2a} represents an aromatic hydrocarbon group which may be substituted; and

R^{3a} represents a pyridyl which may be substituted, or a salt thereof.

16. A compound of claim 15, wherein R^{1a} is an amino which may be substituted by 1 or 2 substituents selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkyl-carbonyl, C_{6-14} aryl-carbonyl and C_{1-6} alkyl-carbamoyl;

R^{2a} is a phenyl which may be substituted by 1 to 3 substituents selected from the group consisting of

halogen atoms, optionally halogenated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy; and

R^{3a} is a pyridyl.

17. A process for producing of a compound of Claim 15, which comprises reacting a compound of the formula:

$$R^{2a}-\underset{\underset{Hal}{|}}{CH}-COR^{3a}$$

wherein Hal represents halogen atoms and other symbols are as defined in claim 15, or a salt thereof with a compound of the formula:

$$R^{1a}-\underset{\underset{S}{\|}}{C}-NH_2$$

wherein R^{1a} is as defined in claim 15, or a salt thereof, optionally in the presence of a base.

18. A pharmaceutical composition which comprises a compound of claim 15.

19. A composition of claim 18 which is an agent for antagonizing adenosine at adenosine A_3 receptors.

20. A composition of claim 18 which is for preventing and/or treating asthma or allergosis.

21. A method for preventing and/or treating diseases related to adenosine A_3 receptor in mammal, which comprises administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable excipient, carrier or diluent.

22. Use of a compound of claim 1 or a salt thereof for manufacturing a pharmaceutical composition for preventing and/or treating diseases related to adenosine A_3 receptor.

SEQUENCE LISTS

Sequence No. : 1
Length: 34 base pairs
Type: nucleic acid
Strandedness: single
Topology: linear
Sequence Type: synthetic DNA
Sequence: CGCCTCTAGA CAAGATGCCC AACAACAGCA CTGC

Sequence No. : 2
Length: 34 base pairs
Type: nucleic acid
Strandedness: single
Topology: linear
Sequence Type: synthetic DNA
Sequence: CGGGGTCGAC ACTACTCAGA ATTCTTCTCA ATGC

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 98/04837

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 149 884 A (TAKEDA CHEMICAL INDUSTRIES LTD) 31 July 1985 see the whole document	1-22
X	WO 93 21168 A (MERCK FROSST CANADA INC) 28 October 1993 see abstract see page 15, line 25 - page 16, line 23 see page 42, line 15 - page 48, line 18; claims 1-14; table 1	1-4, 7-10, 12-15, 18-22

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 1999	07/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	A. Jakobs

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DE 36 01 411 A (NATTERMANN A & CIE) 23 July 1987 see abstract see page 2, line 60 - page 3, line 11 see page 3, line 44 - page 4, line 27; examples 1-8	1-4, 7-10, 12-15, 18-22
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X	WO 97 35856 A (SMITHKLINE BEECHAM CORP ;FEUERSTEIN GIORA Z (US)) 2 October 1997 see page 15, line 15-17; claims 5-13	2,3,9,10
X	WO 97 35855 A (SMITHKLINE BEECHAM CORP ;FEUERSTEIN GIORA Z (US)) 2 October 1997 see page 15, line 15 - page 18, line 34; claims 2-13	2,3,9,10
X	WO 93 15071 A (SMITHKLINE BEECHAM INTERCREDIT) 5 August 1993 see abstract; claims 1-10; examples 1-9	2,3, 8-10,12
X,P	WO 98 21957 A (CHANG LINDA L ;MERCK & CO INC (US)) 28 May 1998 see page 6; examples 1,2,4 see page 41, line 12 - page 48, line 24	1,2, 12-14
X,P	US 5 783 664 A (GALLAGHER TIMOTHY F ET AL) 21 July 1998 see abstract; figure 6	1,2
X	C D NICHOLSON: "Differential modulation of tissue function and therapeutic potential of selective inhibitors of cyclic nucleotide phosphodiesterase isoenzymes" TRENDS IN PHARMACOLOGICAL SCIENCES, vol. 12, no. 1, 1 January 1991, pages 19-27, XP002012152 see table 1	1,14
X	WO 95 11681 A (MERCK & CO INC ;UNIV VIRGINIA (US); DOYLE MICHAEL P (US); JACOBSON) 4 May 1995 see abstract	1,14

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	MANNING A M ET AL: "Transcription inhibitors in inflammation" EXPERT OPINION ON INVESTIGATIONAL DRUGS, vol. 6, no. 5, 1 January 1997, pages 555-567, XP002093379 see abstract; figure 2	1,14
A	DE 28 56 909 A (SCHERING AG) 17 July 1980 see the whole document	1-22
A	STRAPPAGHETTI, GIOVANNELLA ET AL: "Adenosine receptors: synthesis, structure-activity relationships and biological activity of new 6-aminopurine derivatives" EUR. J. MED. CHEM. (1998), 33(6), 501-508 CODEN: EJMCA5;ISSN: 0223-5234, XP002102674 see the whole document	1

International application No.

PCT/JP 98/04837

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 21
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds, which are defined by the general definition(s)/formulae used in claims 1-22, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and / or the compounds mentioned in the claims, and to the general idea underlying the application. (see Guidelines, chapter III, paragraph 2.3)

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/JP 98/04837

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